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(54) Treatment of Raf-mediated cancers with imidazole derivatives

(57) Imidazole derivatives such as 4-[2-(2-chlorophenyl)-5-(3-hydroxyphenyl)-3H-imidazol-4-yl]pyridine antagonise RAF kinase and are useful in the treatment of pancreatic and breast cancers. The compounds may be applied orally in the form of tablets, capsules, liquids or may be applied topically.

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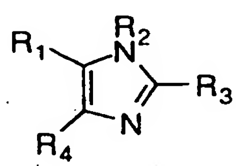
through overexpression include cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung. More particularly, such examples include histiocytic lymphoma, lung adenocarcinoma and small cell lung cancers. Additional examples include cancers in which overexpression or activation of Raf-activating oncogenes (e.g., K-*ras*, *erb*-B) is observed. More particularly, such cancers include pancreatic and breast carcinoma.

The compounds used herein are disclosed in PCT/US94/08297 for use in treating cytokine mediated diseases and cytokine related symptoms. A new use has been discovered for these compounds, treating cancer, in which RAF is implicated.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating cancer which comprises administering to a mammalian patient in need of such treatment an effective amount of a compound of formula (I). Compounds of formula I are represented by the structure:



(I)

wherein:

R_1 is 4-pyridyl, pyrimidinyl, quinazolin-4-yl, quinolyl, isoquinolinyl, 1-imidazolyl or 1-benzimidazolyl which is optionally substituted with one or two substituents each of which is independently selected from C_{1-4} alkyl, halogen, C_{1-4} alkoxy, C_{1-4} alkylthio, $NR_{10}R_{20}$, or N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22};

R_2 is hydrogen, $-(CR_{10}R_{20})_n\ OR_{12}$, heterocyclyl, heterocyclyl C_{1-10} alkyl, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl

m' is a number having a value of 1 or 2;

R_4 is phenyl, naphth-1-yl or naphth-2-yl which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-1-yl substituent, is halo, cyano,-$C(Z)NR_7R_{17}$, -$C(Z)OR_{23}$, -$(CR_{10}R_{20})_{m'''}COR_{36}$, SR_5, -SOR_5, OR_{36}, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, -$ZC(Z)R_{36}$, -$NR_{10}C(Z)R_{23}$ or -$(CR_{10}R_{20})_{m'''}NR_{10}R_{20}$ and which, for other positions of substitution, is halo, cyano, -$C(Z)NR_{16}R_{26}$, -$C(Z)OR_8$, -$(CR_{10}R_{20})_{m'''}COR_8$, -$S(O)_mR_8$, -$OR_8$, halo-substituted-$C_{1-4}$ alkyl, C_{1-4} alkyl, -$(CR_{10}R_{20})_{m''}NR_{10}C(Z)R_8$, -$NR_{10}S(O)_{m'}R_{11}$, -$NR_{10}S(O)_{m'}NR_7R_{17}$, -$ZC(Z)R_8$ or -$(CR_{10}R_{20})_{m'}NR_{16}R_{26}$; wherein m'' is 0 to 5 and m''' is 0 or 1;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties -SR_5 being -SNR_7R_{17} and -SOR_5 being -SOH;

R_6 is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, C_{1-4} alkenyl, C_{2-4} alkynyl or C_{3-5} cycloalkyl;

R_7 and R_{17} are each independently selected from hydrogen or C_{1-4} alkyl, or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22};

R_8 is hydrogen, heterocyclyl, heterocyclylalkyl or R_{11};

R_9 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R_8 and R_9 may together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12};

R_{10} and R_{20} are each independently selected from hydrogen and C_{1-4} alkyl;

R_{11} is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R_{12} is hydrogen, -C(Z)R_{13} or optionally substituted C_{1-4} alkyl, optionally substituted arylC_{1-4} alkyl or $S(O)_2R_{25}$;

R_{13} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl or heteroaryl C_{1-10} alkyl;

R_{14} and R_{24} is each independently selected from hydrogen, alkyl, nitro or cyano;

R_{15} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

R_{16} and R_{26} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12};

R_{18} and R_{19} is each independently selected from hydrogen, C_{1-4} alkyl, substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or together denote a oxygen or sulfur;

R_{21} is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R_{22} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{23} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl or C_{3-5} cycloalkyl;

R_{36} is hydrogen or R_{23};

R_{25} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10} alkyl, heteroaryl or heteroarylalkyl;

R_{27} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl; or a pharmaceutically acceptable salt thereof.

Preferred optionally substituted alkyl groups include, methyl $S(O)_mC_{1-4}$ alkyl- (wherein m is 0, 1 or 2), a methylsulfonamido alkyl-, an aryloxyalkyl-, such as phenoxyalkyl-, or an alkoxyalkyl-, such as ethoxy alkyl, optionally substituted (mono- or di-) amine derivatives include, aminoalkyl-, diethylaminoalkyl, (phenylmethyl-N-methyl)aminoalkyl, (phenylmethyl)amino-1-propyl, or the amino substituents may cyclize to form a 5- to 7-membered heteroring and optionally contain an additional heteroatom, such as a morpholino, pyrrolidinyl, or a piperidinyl group, such as piperidinyl alkyl, pyrrolidinylalkyl, morpholinoalkyl, wherein the alkyl is preferably 1 to 10 carbons in length, more preferably from 1 to 4 carbons, and still more preferably 3 in length. It is recognized that, if the amine derivatives cyclize, the term may overlap that of the heterocyclic alkyl derivatives.

More preferably R_2 is an optionally substituted C_{1-10} alkyl, an optionally substituted heterocyclyl ring, an optionally substituted heterocyclyl C_{1-10} alkyl, an optionally substituted aryl, $(CR_{10}R_{20})_{n'}NR_8R_9$, or $(CR_{10}R_{20})_{n'}C(Z)OR_{13}$ group.

When R_2 is an optionally substituted heterocyclyl C_{1-10} alkyl group, the ring is preferably a morpholino, pyrrolidinyl or a piperidinyl group. Preferably this alkyl moiety is from 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl group. Preferred heterocyclic alkyl groups include, but are not limited to morpholino ethyl, morpholino propyl, pyrrollidinyl propyl and piperidinyl propyl moieties. The heterocyclyl ring may be optionally substituted one to four times independently by halogen; C_{1-4} alkyl; aryl, such as phenyl; aryl alkyl, such as benzyl- wherein the aryl or aryl alkyl moieties themselves may be optionally substituted (as in the definition section above); $C(O)OR_{13}$, such as the $C(O)C_{1-4}$ alkyl or $C(O)OH$ moieties; $C(O)H$; $C(O)C_{1-4}$ alkyl, hydroxy substituted C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl (wherein m is 0, 1, or 2), $NR_{10}R_{20}$ (wherein R_{10} and R_{20} are independently hydrogen or C_{1-4} alkyl).

When R_2 is an optionally substituted heterocyclyl the ring is preferably a morpholino, pyrrolidinyl or a piperidinyl group. When the ring is optionally substituted the substituents may be directly attached to

When R_2 is $(CR_{10}R_{20})_{n'}NR_8R_9$, R_8 and R_9 are as defined in Formula (I), preferably R_8 and R_9 are each independently selected from hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl or an optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12}. It is recognized that, in some instances, this can yield the same moiety as a heterocyclic C_{1-10} alkyl moiety noted above which is also a suitable R_2 variable. Preferably R_8 and R_9 are independently hydrogen, C_{1-4} alkyl, preferably methyl, or benzyl. The n term is preferably 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl group. Preferred groups include, but are not limited to, aminopropyl, (N-methyl-N-benzyl)aminopropyl, (N-phenylmethyl)amino-1-propyl and diethylamino propyl.

When R_2 is a $(CR_{10}R_{20})_{n'}C(Z)OR_{13}$ group, R_{13} is suitably hydrogen or C_{1-4} alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group. Preferred groups include, but are not limited to carboxymethyl-1-butyl, carboxy-1-propyl, or 2-acetoxyethyl.

When R_2 is a $(CR_{10}R_{20})_{n'}S(O)_mR_{25}$ group m is 0, 1 or 2, and R_{18} is preferably aryl, especially phenyl, or C_{1-10} alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl and propyl group.

When R_2 is a $(CR_{10}R_{20})_{n'}OR_{13}$ group, R_{13} is suitably hydrogen, aryl, especially phenyl, or C_{1-10} alkyl, especially methyl or ethyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R_2 is a $(CR_{10}R_{20})_{n'}NHS(O)_2R_{18}$ group, R_{18} is suitably alkyl, especially methyl. Then n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R_2 is an optionally substituted aryl, the aryl is preferably phenyl. The aryl ring may be optionally substituted one or more times, preferably by one or two substituents, independently selected from C_{1-4} alkyl, halogen, especially fluoro or chloro, $(CR_{10}R_{20})_tOR_{13}$,

5-(R_{18})-1,2,4-oxadiazol-3-yl and 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl.

Preferred substituents Y_1 for use in R_3 when the aryl or heteroaryl group Q is mono-substituted include -$(CR_{10}R_{20})_nY_2$ wherein: n is 0, 1, 2 or 3, preferably 0 or 1; and Y_2 is -OR_8, especially where R_8 is hydrogen or C_{1-10} alkyl; -NO_2; -$S(O)_{m'}R_{11}$, especially where R_{11} is C_{1-10} alkyl; -SR_8, especially when R_8 is C_{1-10} alkyl; -$S(O)_mNR_8R_9$, especially where R_8 and R_9 is each hydrogen or C_{1-10} alkyl or R_8 and R_9 together with the nitrogen to which they are attached form a 5 to 7 membered ring which optionally includes another heteroatom selected from oxygen, sulfur or NR_{12} and m is 2; n' is 1 to 10; -NR_8 R_9, especially when R_8 and R_9 is each hydrogen, methyl or benzyl or R_8 and R_9 together with the nitrogen to which they are attached form a 5 to 7 membered ring which optionally includes another heteroatom selected from oxygen, sulfur or NR_{12}; -O $(CR_{10}R_{20})_nNR_8R_9$, especially where R_8 and R_9 is each C_{1-10} alkyl; -$C(O)R_8$, especially where R_8 is hydrogen or C_{1-10} alkyl; -CO_2R_8, especially where R_8 is hydrogen or C_{1-10} alkyl; -CO_2 $(CR_{10}R_{20})_{n'}CONR_8R_9$, especially where R_8 and R_9 is hydrogen or C_{1-10} alkyl; -CN; -$C(Z)NR_8R_9$, especially where R_8 and R_9 is hydrogen or C_{1-10} alkyl; -$NR_{10}S(O)_mR_{11}$, especially where R_{10} is hydrogen or C_{1-10} alkyl and R_{11} is C_{1-10} alkyl or a halo-substituted alkyl; -$NR_{10}C(Z)R_8$, especially where R_8 is C_{1-10} alkyl and R_{10} is hydrogen and Z is oxygen; -$C(Z)NR_8OR_9$, especially where R_8 and R_9 is each hydrogen and Z is oxygen; -$NR_{10}C(Z)NR_8R_9$, especially where R_8 and R_9 is each hydrogen or C_{1-10} alkyl and Z is oxygen; -$N(OR_{21})C(Z)NR_8R_9$, especially where R_8, R_9 and R_{21} is each hydrogen or C_{1-10} alkyl and Z is oxygen; -$C(=NOR_{13})NR_8R_9$, especially where R_8, R_9 and R_{13} is each hydrogen; -$NR_{10}C(=NR_{15})NR_8R_9$, especially where R_8 and R_9 is hydrogen, C_{1-10} alkyl or arylalkyl and R_{15} is cyano; and 5-(R_{18})-1,2,4-oxadiazol-3-yl and 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl, especially where R_{12} is hydrogen and R_{18} and R_{19} is each hydrogen or C_{1-10} alkyl or together are oxo.

substituted C_{3-7} cycloalkyl, or an optionally substituted C_{3-7} cycloalkyl C_{1-10} alkyl, an optionally substituted aryl, an optionally substituted heterocyclic alkyl, an optionally substituted heterocyclic, optionally substituted heteroaryl or heteroarylalkyl, $(CR_{10}R_{20})_{n'}OR_{13}$, $(CR_{10}R_{20})_{n'}S(O)_mR_{25}$, $(CR_{10}R_{20})_{n'}NR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)OR_{13}$, $(CR_{10}R_{20})_{n'}NHS(O)_2R_{25}$, $(CR_{10}R_{20})_{n'}C(Z)R_{13}$, or $(CR_{10}R_{20})_{n'}C(=NOR_{21})R_{13}$; and R_1, R_3 and R_4 are as defined for formula (I).

More preferred are those compounds wherein R_2 is a C_{1-4} alkyl (branched and unbranched), such as isopropyl, butyl, t-butyl, n-propyl, a methylthio propyl, a methylsulfinyl propyl, an amino propyl, N-methyl-N-benzylamino propyl group, (phenylmethyl)amino-1-propyl, diethylamino propyl, cyclopropyl methyl, morpholinyl butyl, morpholinyl propyl, morpholinyl ethyl, 1-formyl-4-piperidinyl, 1-benzyl-4-piperidinyl, 1-methyl-4-piperidinyl, 1-ethoxycarbonyl-4-piperidinyl, phenyl substituted by halogen, thioalkyl or sulfinyl alkyl such as a methylthio, methylsulfinyl or a methylsulfonyl moiety; and R_1, R_3 and R_4 are defined for Formula (I).

Further preferred compounds of Formula (I) are those wherein R_1 is an optionally substituted 4-pyridyl or pyrimidinyl; and more preferably R_4 is a 2-methyl-4-pyridyl or 2-amino-pyrimidinyl.

Other groupings include those where R_2 is hydrogen, and R_3 is a 2- or 3-thiophene, or a substituted phenyl wherein the substituents are selected from methyl thio, methylsulfinyl, methylsulfonyl, methoxy, N-morpholinomethyl, $-CH_2NH_2$ or $-C(=NOH)NH_2$; provided that when R_4 is phenyl, the methylthio, methylsulfinyl, methylsulfonyl groups are in the 2- or 3-position of the phenyl ring; and R_4 is a halo-substituted phenyl, naphth-1-yl, or naphth-2-yl; or a pharmaceutically acceptable salt thereof.

Most preferred are those compounds wherein R_2 is other than hydrogen, when R_4 is an unsubstituted 4-pyridyl and R_3 is substituted phenyl.

Exemplified compounds herein include:

4-[4-(4-Fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]benzamidoxime;

4-pyridyl or 4-pyrimidinyl group and the optional substituent is selected from alkyl, amino and mono- or di-alkyl amino.

Another embodiment of the invention is a method of treating cancer as described above wherein R_2 is an optionally substituted heterocyclic or heterocyclic alkyl moiety.

A further embodiment of the invention is a method of treating cancer as described above, wherein R_2 is an optionally substituted heterocyclic or heterocyclic alkyl moiety, and R_2 is morpholino, pyrrolidinyl, piperidinyl group, piperidinylalkyl, pyrrolidinylalkyl, morpholinoalkyl or phenoxyalkyl, all of which any be optionally substituted with ethoxyalkyl, aminoalkyl, diethylamino, (phenylmethyl-N-methyl)aminoalkyl, or (phenylmethyl)amino-1- propyl.

Yet another embodiment of the invention is a method of treating cancer as described above wherein R_2 is 1-formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine or 1-ethoxycarbonyl-4-piperidine.

Another embodiment of the invention is a method of treating cancer as described above wherein in R_3, the group Q comprises an optionally substituted pheny or thienyl moiety.

A further embodiment of the invention is a method of treating cancer as described above wherein the substituent Q is phenyl substituted by halogen, halosubstituted alkyl or $-(CR_{10}R_{20})_nY_2$ wherein Y_2 is $-OR_8$, $-S(O)'R_{11}$, $-SR_8$, $-S(O)_mNR_8R_9$, or $-NR_8R_9$.

Another embodiment of the invention is a method of treating cancer as described above wherein R_4 is optionally substituted phenyl, naphth-1-yl or naphth-2-yl, wherein the phenyl, 4-naphth-1-yl or 5-naphth-2-yl moiety are substituted by one or two substituents each independently selected from halogen, $-SR_5$, $-SOR_5$, $-OR_{36}$, or

R_{36} is hydrogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-5} cycloalkyl,

or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is method of treating cancer as described above wherein the compound administered is selected from the group consisting of:

4-[2-(2-Chlorophenyl)-5-(3-hydroxyphenyl)-3H-imidazol-4-yl]pyridine;
4-[4-(4-Fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]benzamidoxime;
4-(1-Naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(1-Naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(2-Naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(2-Naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-thiophene)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-thiophene)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole; and pharmaceutically acceptable salts thereof.

A further embodiment of the invention is a method of treating cancer as described above wherein the compound administered is 4-[2-(2-chlorophenyl)-5-(3-hydroxyphenyl)-3H-imidazol-4-yl]pyridine.

Yet another embodiment of the invention is a method of treating cancer as described above wherein the compound administered is: 4-(3-hydroxyphenyl)-2-(2-chlorophenyl)-5-(4-pyridyl) imidazole.

Suitable pharmaceutically acceptable salts are well known

cation No. PCT/US94/08297. Thes describe the synthesis of α-diketones and α-hydroxyketones (benzoins) and their subsequent use in preparing imidazoles and N-hydroxyl imidazoles. Thereafter, further compounds of formula (I) may be obtained by manipulating substituents in any of the groups R_1, R_2, R_3 and R_4 using conventional functional group interconversion procedures.

In particular, in a first process, compounds of formula (I) may be prepared by condensing an α-diketone of formula (II):

R_1COCOR_4 (II)

wherein R_1 and R_4 are as hereinbefore defined, or an equivalent thereof, with an aldehyde of the formula (III):

R_3CHO (III)

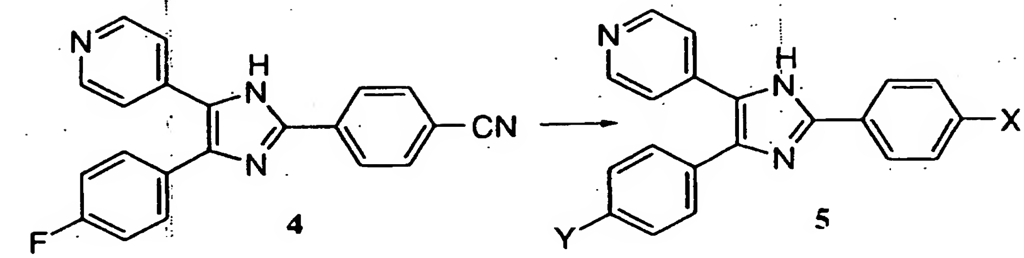
wherein R_3 is as hereinbefore defined, or an equivalent thereof, and, if necessary, with ammonia or a source thereof, under imidazole-ring forming conditions.

Suitable equivalents of the α-diketone are well known to those skilled in the art and include the corresponding α–keto-oxime and α-dioxime. Suitable equivalents of the aldehyde of formula (III) are well known in the art and include the corresponding oxime and acetal.

Ammonia, or a source thereof, is preferably used in excess, with at least a dimolar amount being used in the case of the α-diketone and at least an equimolar amount in the case of the α-keto-oxime.

Suitable sources of ammonia include ammonium salts of organic carboxylic acids, such as an ammonium C_{1-6} alkanoate, for instance ammonium acetate and ammonium formate, preferably ammonium acetate, and carboxylic amides, in particular of formic acid, such as formamide. An ammonium salt is generally used in large excess and in the presence of an acid, such as a C_{1-6} carboxylic acid which acid may also be used as a solvent for the reaction. If formamide is used, this may be used in excess as the reaction solvent. An alternative solvent such as ethanol or dimethyl sulphoxide (Lantos, et al., J. Het. Chem. **19**, 1375, 1982) may be used. An additional solvent may also be employed, for instance dimethyl formamide may be used with formamide. The reaction is generally carried out at elevated temperatures, for instance

In Scheme I, the anion prepared from **1**, by treatment with a strong base such as lithium di-*iso*-propylamide, is condensed with substituted benz-aldehyde, to give, after removal of the protecting group, the diol **2**. This may then be converted to the α-diketone **3** by a Swern oxidation of which any number of potentially useful variations are known and may be used. The α-diketone **3** is then cyclized to an imidazole **4**, a compound of formula (I), by heating **3** with a substituted benzaldehyde in a mixture of ammonium acetate, as the source of ammonia, and an appropriate solvent, for example acetic acid or DMSO. The imidazole **4** may then be transformed into other imidazoles **5** by appropriate functions group interconversion procedures. Scheme I also illustrates the preparation of a protected α-hydroxyketone **2a**, by condensing the anion of **1** with an appropriately activated carbonyl derivative of a substituted benzamide, such as the N-methoxy-N-methylamide, to yield a protected α-hydroxyketone. This adduct **2a** may then be directly converted to the imidazole **5**, using a combination of a copper (II) salt, such as copper (II) acetate, as an oxidizing agent and ammonium acetate as a source of ammonia. The α-hydroxyketone **2a** may also be deprotected and then oxidized to give an α-diketone **3**, for instance using Swern oxidation.



$X = CO_2R, CH_2NR_2, CONR_2, CH_2NSO_2R$
$Y = F, S(O)_nMe,$
$n = 0\text{-}2$

Scheme II illustrates the use of an α-keto-oxime for preparing a compound of formula (I). A heterocyclic ketone **7** is prepared by adding the anion of 4-methyl-quinoline (prepared by treatment thereof with an alkyl lithium, such as n-butyl lithium) to an N-alkyl-O-alkoxybenzamide. Alternatively, the anion may be condensed with a benzaldehyde, to give an alcohol which is then oxidized to the ketone **7**. The α-keto-oxide **8** is then prepared from **7** using standard conditions, such as reaction with sodium nitrite, and this may then be reacted with a benzaldehyde to afford an N-hydroxyimidazole **9**, a compound of formula (I) in which R_2 is hydroxy. This may be converted to **10**, a further compound of formula (I) in which R_2 is hydrogen, by treating it with a deoxygenating agent such as phosphorus trichloride or a trialkyl phosphite, such as trimethyl or triethylphosphite. For compounds of formula (I) wherein R_3 is $-(CR_{10}R_{20})_n-P(Z)-(X_bR_{13})_2$, the reagent $OHC-(CR_{10}R_{20})_n-P(Z)-(X_bR_{13})_2$ may be used instead of $OHC-C_6H_4-X$ to make the appropriately substituted compound **9**.

formula (III) or an equivalent thereof, and a source of ammonia. Suitable oxidizing agents include, for example, an oxidizing heavy metal salt, preferably an organic copper (II) salt, such as copper (II) acetate or copper (II) citrate. The reaction may be effected in a solvent such as acetic acid, under reflux conditions. Alternatively, a lower alkanol solvent, such as methanol or ethanol, may be used, preferably at a temperature in the region of from 30 to 100°C (see The Chemistry of Heterocyclic Compounds, Imidazole and its derivatives, part I, ed. Weissberger, Interscience Publishers, Inc., New York, 1953, 38). This approach is also illustration in Scheme I.

In a further process, a compound of formula (I) may be obtained by treatment with a compound of formula (XI) as described later. A compound of Formula (XI) is obtained by treating a compound (an amidine) of formula (IV):

$$R_3C(=NH)NHR_2 \qquad (IV)$$

wherein R_2 and R_3 are as hereinbefore defined, or a salt thereof, with a reactive ester of an α–hydroxyketone of formula (IIA) or the corresponding α-haloketone, in an inert solvent such as a halogenated hydrocarbon solvent, for example chloroform, at a moderately elevated temperature and, if necessary, in the presence of a suitable condensation agent such as a base. Suitable reactive esters include esters of strong organic acids such as a lower alkane sulphonic or aryl sulphonic acid, for instance methane or *p*-toluene sulphonic acid. The amidine of formula (IV) is preferably used as the salt, suitably the hydrochloride salt, which may then be converted into the free amidine *in situ*, by employing a two-phase system in which the reactive ester is in an inert organic solvent such as chloroform, and the salt is in an aqueous phase to which a solution of an aqueous base is slowly added, in dimolar amount, with vigorous stirring. Suitable amidines of formula (IV) may be obtained by standard methods, see for instance Garigipati R. Tetrahedron Letters, 190 31, 1989.

Compounds of Formula (IV) wherein R^2 is methyl, for instance may be made by the route indicated below.

In a further process, N-substituted compounds of formula (I) may be prepared by treating the anion of an amide of formula (VII):

$R_1CH_2NR_2COR_3$ (VII)

wherein R_1 and R_3 are as hereinbefore defined and R_2 is as hereinbefore defined other than hydrogen, with:

(a) a nitrile of the formula (VIII):

R_4CN (VIII)

wherein R_4 is as hereinbefore defined, or

(b) an excess of an acyl halide, for instance an acyl chloride, of the formula (IX):

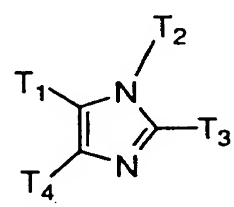
R_4COHal (IX)

wherein R_4 is as hereinbefore defined and Hal is halogen, or a corresponding anhydride, to give a *bis*-acylated intermediate which is then treated with a source of ammonia, such as ammonium acetate.

This approach permits the regiospecific preparation of compound of formula (I) substituted at the 1-position, as illustrated in Scheme III. A primary amine RNH_2 is treated with 4-chloromethylpyridine to give **11** which is then converted to the amide **12** by standard techniques. Deprotonation of **12** with a strong amide base, such as lithium di-*iso*-propyl amide or sodium *bis*-(trimethylsilyl)amide, followed by addition of an excess of an aroyl chloride yields the *bis*-acylated compound **13** which is then closed to an imidazole compound of formula (I), **14**, by heating in acetic acid containing ammonium acetate. Alternatively, the anion of **12** may be reacted with a substituted aryl nitrile to produce the amidazole **14** directly.

R_3COHal wherein R_3 is as hereinbefore defined, or the corresponding anhydride, under standard acylating conditions.

In a further process, compounds of formula (I) may be prepared by coupling a suitable derivative of a compound of formula (XI):



(XI)

wherein T_2 is a nitrogen protecting group or R_2, other than hydrogen; and T_1 is hydrogen, T_3 is Q and T_4 is R_4; T_1 is R_1, T_3 is hydrogen and T_4 is R_4; or T_1 is R_1, T_3 is Q and T_4 is hydrogen, in which R_1, R_2, R_3, R_4 and Q are as hereinbefore defined; with (i) when T_1 is hydrogen, a suitable derivative of the heteroaryl ring R_1H, under ring coupling conditions, to effect coupling of the heteroaryl ring R_1 to the imidazole nucleus at position 5; (ii) when T_3 is hydrogen, a suitable derivative of the aryl or heteroaryl ring QH, under ring coupling conditions, to effect coupling of the ring Q to the imidazole nucleus at position 2; or (iii) when T_4 is hydrogen, a suitable derivative of the aryl ring R_4H, under ring coupling conditions, to effect coupling of the aryl ring R_4 to the imidazole nucleus at position 4.

Such aryl/heteroaryl coupling reactions are well known to those skilled in the art. In general, an organometallic synthetic equivalent of an anion of one component is coupled with a reactive derivative of the second component, in the presence of a suitable catalyst. The anion equivalent may be formed from either the imidazole of formula (XI), in which case the aryl/heteroaryl compound provides the reactive derivative, or the aryl/heteroaryl compound in which case the imidazole provides the reactive derivative. Accordingly, suitable derivatives of the compound of formula (XI) or the aryl/heteroaryl rings include organometallic derivatives such as organomagnesium, organozinc, organostannane and boronic acid derivatives and suitable reactive derivatives include the

formamide. Trilkyltin derivatives may be conveniently obtained by metallation of the corresponding compound of formula (XI) with a lithiating agent, such as *s*-butyl-lithium or *n*-butyllithium, in an ethereal solvent, such as tetrahydrofuran, or treatment of the bromo derivative of the corresponding compound of formula (XI) with an alkyl lithium, followed, in each case, by treatment with a trialkyltin halide. Alternatively, the bromo- derivative of a compound of formula (XI) may be treated with a suitable heteroaryl or aryl trialkyl tin compound in the presence of a catalyst such as *tetrakis*-(triphenyl-phosphine)-palladium, under conditions similar to those described above.

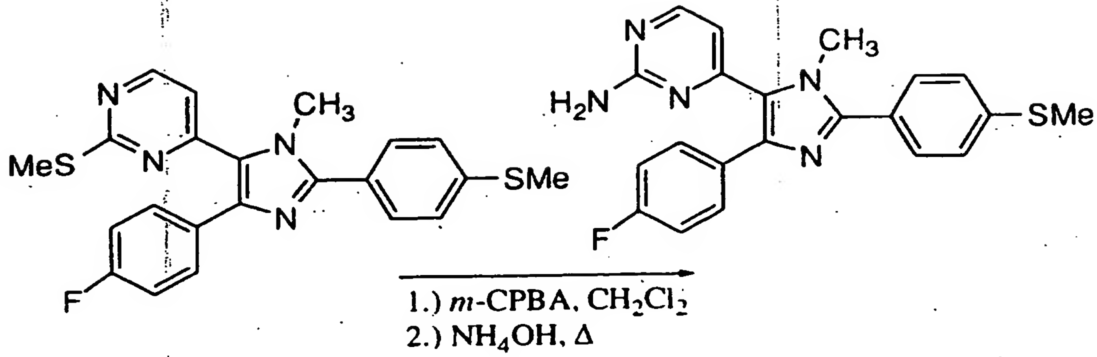
Boronic acid derivatives are also useful. Hence, a suitable derivative of a compound of formula (XI), such as the bromo, iodo, triflate or fluorosulphonate derivative, may be reacted with a heteroaryl- or aryl-boronic acid, in the presence of a palladium catalyst such as *tetrakis*-(triphenylphosphine)-palladium or $PdCl_2$[1,4-*bis*-(diphenyl-phosphino)butane] in the presence of a base such as sodium bicarbonate, under reflux conditions, in a solvent such as dimethoxyethane (see Fischer and Haviniga, Rec. Trav. Chim. Pays Bas, **84**, 439, 1965, Snieckus, V., Tetrahedron Letters, **29**, 2135, 1988 and Terashimia, M., Chem. Parm. Bull., **11**, 4755, 1985). Non-aqueous conditions, for instance, a solvent such as DMF, at a temperature of about 100°C, in the presence of a Pd(II) catalyst may also be employed (see Thompson W. J., et al., J. Org. Chem., **49**, 5237, 1984). Suitable boronic acid derivatives may be prepared by treating the magnesium or lithium derivative with a trialkylborate ester, such as triethyl, tri-*iso*-propyl or tributylborate, according to standard procedures.

In such coupling reactions, it will be readily appreciated that due regard must be exercised with respect to functional groups present in the compounds of formula (XI)). Thus, in general, amino and sulfur substituents should be non-oxidized or protected and the N-1 nitrogen of a compound of formula (XI) be protected, if an NH compound is finally required. Nitro, bromo, iodo and hydroxyl groups should preferably be avoided in compounds of formula (XI) in which T_1 is hydrogen.

or solvent mixture, such as decalin, decalin and diglyme, *p*-cymene, xylene or mesitylene, under reflux conditions, or preferably, potassium *t*-butoxide in *t*-butanol with dry air or oxygen.

Once the imidazole nucleus has been established, further compounds of formula (I) which may be prepared by applying standard techniques for functional group interconversion, for instance: $-C(O)NR_8R_9$ from $-CO_2CH_3$ by heating with or without catalytic metal cyanide, e.g. NaCN, and HNR_8R_9 in CH_3OH; $-OC(O)R_8$ from -OH with e.g. $ClC(O)R_8$ in pyridine; $-NR_{10}-C(S)NR_8R_9$ from $-NHR_{10}$ with an alkylisothiocyante or thiocyanic acid; $NR_6C(O)OR_6$ from $-NHR_6$ with the alkyl chloroformate; $-NR_{10}C(O)NR_8R_9$ from $-NHR_{10}$ by treatment with an isocyanate, e.g. HN=C=O or $R_{10}N=C=O$; $-NR_{10}-C(O)R_8$ from $-NHR_{10}$ by treatment with $Cl-C(O)R_8$ in pyridine; $-C(=NR_{10})NR_8R_9$ from $-C(NR_8R_9)SR_8$ with $H_3NR_8^+OAc^-$ by heating in alcohol; $-C(NR_8R_9)SR_8$ from $-C(S)NR_8R_9$ with R_6-I in an inert solvent, e.g. acetone; $-C(S)NR_8R_9$ (where R_8 or R_9 is not hydrogen) from $-C(S)NH_2$ with HNR_8R_9, $-C(=NCN)-NR_8R_9$ from $-C(=NR_8R_9)-SR_8$ with NH_2CN by heating in anhydrous alcohol, alternatively from $-C(=NH)-NR_8R_9$ by treatment with BrCN and NaOEt in EtOH; $-NR_{10}-C(=NCN)SR_8$ from $-NHR_{10}$ by treatment with $(R_8S)_2C=NCN$; $-NR_{10}SO_2R_8$ from $-NHR_{10}$ by treatment with $ClSO_2R_8$ by heating in pyridine; $-NR_{10}C(S)R_8$ from $-NR_{10}C(O)R_8$ by treatment with Lawesson's reagent [2,4-*bis*(4-methoxyphenyl)-1,3,2,4,-dithiadiphosphetane-2,4-disulfide]; $-NR_{10}SO_2CF_3$ from $-NHR_6$ with triflic anhydride and base; $-NR_{10}C(O)-C(O)-OR_8$ from $-NHR_{10}$ with, e.g. methyloxalyl chloride and a base such as triethylamine; $-NR_{10}C(O)-C(O)-NR_8R_9$ from $-NR_{10}C(O)-C(O)-OR_8$ with HNR_8R_9; and 1-(NR_{10})-2imidazolyl from $-C(=NH)NHR_{10}$ by heating with 2-chloroacetaldehyde in chloroform (wherein R_6, R_8, R_9 and R_{10} are as hereinbefore defined).

Compounds of formula (I) in which R_2 is hydrogen may be readily converted into further compounds of formula (I) in which R_2 is other than hydrogen, for instance alkyl, by conventional procedures such as alkylation or acylation followed by reduction. Such methods are in general relatively inefficient as they lack regiospecificity and the desired



Suitable protecting groups for use with hydroxyl groups and the imidazole nitrogen as well known in the art and described in many references, for instance Protecting Groups in Organic Synthesis (2d ed), Greene T. W., Wiley-Interscience, New York, (1991). Suitable examples of hydroxyl protecting groups include silyl ethers, such as t-butyl-dimethyl or t-butyldiphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link, $(CR_{10}R_{20})_{n'}$ as defined in formula (I). Suitable examples of imidazole nitrogen protecting groups include tetrahydropyranyl.

It should be noted that the compounds of formula (I), where R_4 may be an alkylsulfinyl, arylsulfinyl, alkylsulfonyl, or arylsulfonyl are prodrugs which are reductively converted in vivo to the corresponding alkylthio or arylthio form.

Pharmaceutically acid addition salts of compounds of formula (I) may be obtained by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

for 1.5 hours. The mixture is poured into a solution of NH_4Cl (98 g) and H_2O (500 mL), then extracted with EtOAc (3 x 250 mL). The EtOAc extracts are washed with H_2O and saturated NaCl, then dried over $MgSO_4$. Evaporation of the solvent *in vacuo* affords the title compound (114.2 g).

(b) 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

To a solution of 1-(t-butyldimethylsilyloxy)-2-(4-fluorophenyl)-1-(4-pyridyl)ethanone (6.3 g, 18.3 mmol) in glacial acetic acid (125 mL) is added anhydrous copper (II) acetate (6.6 g, 36.5 mmol), ammonium acetate (14 g, 183 mmol) and 4-(methylthio)benzaldehyde (3.5 g, 22.9 mmol) and the mixture is heated at reflux. After 1 hour, the reaction is cooled then poured into a mixture of conc. NH_4OH (175 mL), ice (100 mL) and EtOAc (100 mL). The resulting mixture is stirred for 15 minutes, then the layers separated. The aqueous layer is extracted with EtOAc (2 x 50 mL). The combined EtOAc extracts are washed and saturated NaCl and dried over $MgSO_4$. Evaporation of solvent *in vacuo* gives an oil which is taken up in acetone. 3 N HCl is added dropwise to adjust the pH to 2-3; and the resulting solid is filtered.

EXAMPLE 3

4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole

To a solution of 4-(4-fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole (0.80 g, 2.2 mmol) [See Ex. 2 above.] in glacial acetic acid (15 mL) is added a solution of $K_2S_2O_8$ (0.72 g, 2.6 mmol) in H_2O (20 mL). Additional glacial acetic acid (15 mL) is added to ensure homogeneity, and the resulting solution is stirred at rt for 18 hours. The mixture is then poured into H_2O, and the pH adjusted to neutral by the addition of conc. NH_4OH. The solid which forms is

The title compound is prepared using the same procedure as described in Example 3, except using 4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole.

EXAMPLE 7

4-(4-Fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 2, except using 4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole.

EXAMPLE 8

4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 2(b), except using 2-(methylthio)-benzaldehyde.

EXAMPLE 9

4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 3, except using 4-(4-Fluorophenyl)-2-(2-methylthiophenyl)-5-(4-pyridyl)-1H- imidazole.

EXAMPLE 10

4-(4-Fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)-1H-imidazole

EXAMPLE 15

4-(naphth-1-yl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 3, except using 4-(naphth-1-yl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole.

EXAMPLE 16

4-(naphth-2-yl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 3, except using 4-(naphth-2-yl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole.

EXAMPLE 17

2-(4-Cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 2(b), except using 4-cyanobenzaldehyde.

EXAMPLE 18

2-(4-Aminomethylphenyl)-4-phenyl-5-(4-pyridyl)-imidazole

To a solution of 2-(4-cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole (2.5 g, 7.3 mmol) [See Ex. 17 above.] in THF (50 mL) is added $LiAlH_4$ (7.3 mL of 1 M solution in THF, 7.3 mmol). The resulting mixture is heated at reflux for 2 hours. Additional $LiAlH_4$ (4.0 mL 4.0 mmol) is added and heating was continued for 30 minutes. The mixture is allowed to cool, then poured into 2.5 N NaOH and extracted with THF. The organic extract is washed and saturated aqueous NaCl and concentrated under reduced pressure. The residue is purified by flash

(d) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylsulfinyl) phenyl-5-(4-pyridyl)imidazole

The title compound is prepared by the same procedure as described in Example 20 except using 4-(4-fluoro)phenyl-1-methyl-2-(4-methylthio) phenyl-5-(4-pyridyl)imidazole.

EXAMPLE 21

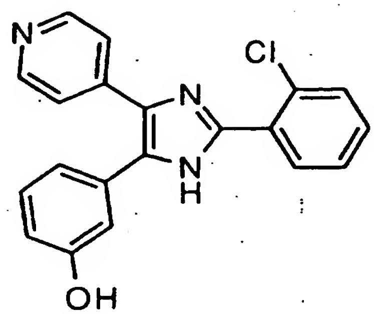
4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenyl-5-[4-(2-amino)-pyrimidinyl]imidazole

(a) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methythio) phenyl-5-tri-n-butylstannylimidazole

The title compound is prepared by the procedure of Bender, et al. (U.S. Patents 5,145,858 and 5,002,941) except using 4-(4-fluoro)phenyl-1-methyl-2-(4-methylthio)phenylimidazole.

(b) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenyl-5-[4-(2-methylthio)pyrimidinyl]imidazole

A mixture of 4-(4-Fluoro)phenyl-1-methyl-2-(4-methythio)phenyl-5-tri-n-butylstannylimidazole (0.25 g, 0.42 mmol), 4-iodo-2-methythiophenylpyrimidine (0.16 g, 0.63 mmol) [prepared by the procedure of Majeed, et al. (Tetrahedron 1989, 45(4), 993)] and bis(triphenylphosphine)-palladium (II) dichloride (0.30 g, 0.42 mmol) in 1,2 dichloroethane (10 mL) is heated to reflux for 24 hours. The reaction mixture is cooled to ambient temperature and a solution of saturated potassium fluoride in methanol (2 mL) is added. After stirring for 1 hour at ambient temperature, the mixture is poured into water and extracted twice with dichloromethane. The organic layers are combined, washed with saturated aqueous sodium chloride, dried ($MgSO_4$) the solvent evaporated. The residue is purified by flash chromatography eluting with dichloromethane to afford the title compound (0.14 g).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N
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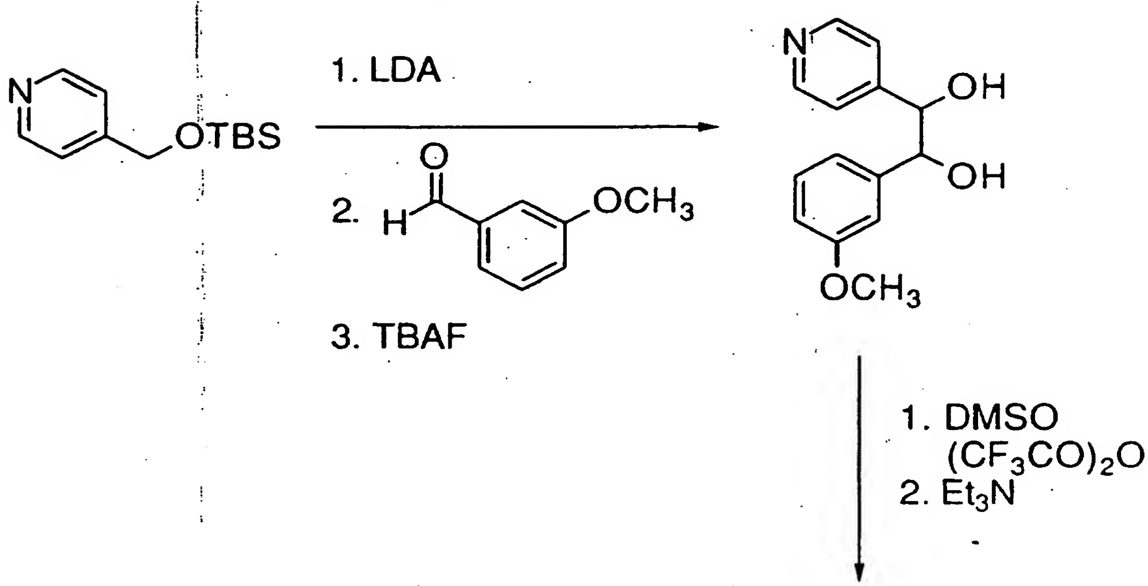

N
OTBS
1. LDA
2. H OCH3
3. TBAF
N
OH
OH
OCH3
1. DMSO
(CF3CO)2O
2. Et3N

reduced pressure. The resulting oil was dissolved in tetrahydrofuran (120 mL) and to this solution was added tetrabutylammonium fluoride (48 mL of a 1.0 M solution in tetrahydrofuran) dropwise. After ten minutes, the reaction mixture was concentrated at reduced pressure and the resulting oil was chromatographed on silica gel eluting with 97:3 ethyl acetate:methanol to give a mixture of diastereomeric diols as a foam (8.5 g) which was used without further purification.

Step B

1-(3-Methoxyphenyl)-2-pyridin-4-yl-ethane-1,2-dione

To a stirring solution fo methyl sulfoxide (11.8 g, 10.7 mL, 150 mmol) in dichloromethane (150mL) at -78°C was added trifluoroacetic anhydride (23.7 g, 16 mL, 113 mmol) dropwise. After ten minutes, 1-(3-Methoxyphenyl)-2-pyridin-4-yl-ethane-1,2-diol (8.5 g, 34 mmol) in dichloromethane (60 mL) was added dropwise. Ater another ten minutes, triethylamine (21.3 g, 29.4 mL, 211 mmol) was added dropwise and the reaction mixture was immediately warmed to 0°C and then poured into saturated aqueous sodium hydrogen carbonate (300 mL). The aqueous layer was extracted with ethyl acetate (3x200 mL) and the organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting oil was chromatographed on silica gel eluting with 1:3 ethyl acetate:hexane to give the dione as a yellow solid (5.1 g).

^{1}H NMR (300MHz,$CDCl_3$) δ 8.88 (dd, J = 4.4 and 2.5 Hz, 2H), 7.77 (dd, J= 4.4 and 2.5 Hz, 2H), 7.56-7.51 (m, 1H), 7.50-7.39 (m, 2H), 7.22-7.19 (m, 1H), 3.85 (s, 3H).

Step C

4-[2-(2-Chlorophenyl)-5-(3-methoxyphenyl)-3H-imidazol-4-yl]pyridine

1-(3-Methoxyphenyl)-2-pyridin-4-yl-ethane-1,2-dione (2.0 g, 8.3 mmol), 2-chlorobenzaldehyde (1.2 g, 0.94 mL, 8.3 mmol) and ammonium acetate (6.4 g, 83 mmol) were dissolved in acetic acid (30 mL) and heated to reflux for 1 hour, then allowed to cool to ambient

The following compounds may be made by analogous methods to those described above:

Example 23: 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;
Example 24: 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;
Example 25: 4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-1-(N-morpholino-propyl)-5-(4-pyridyl)imidazole;
Example 26: 4-(4-Fluorophenyl)-1-(methylthio-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole;
Example 27: 4-(4-Fluorophenyl)-1-(methylsulfinyl-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole;
Example 27: 4-(4-Fluorophenyl)-1-(methylsulfonyl-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole.

In order to use a compound of formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier.

Compounds of formula (I), or pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of formula (I) may be administered in conventional dosage forms prepared by combining a compound of formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of formula (Ib) may be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character

lation. It may, however, comprise as much as 10% w/w, but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; beeswax; a metallic soap; an oil or natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or

skilled in the art using convention led in the art using conventional course of treatment determination tests.

Raf kinase assay

Raf kinase activity *in vitro* is measured by the phosphorylation of its physiological substrate MEK (Map kinase/ERK kinase). Phosphorylated MEK is subsequently trapped on a filter membrane and incorporation of radio-labeled phosphate is quantitated by scintillation counting.

MATERIALS

Activated Raf

Produced in Sf9 insect cells coinfected with three different baculoviruses expressing epitope-tagged Raf, and the upstream activators Val^{12}-H-Ras, and Lck. The epitope sequence Glu-Tyr-Met-Pro-Met-Glu ("Glu-Glu") was fused to the carboxy-terminus of full-length c-Raf.

MEK

Catalytically inactive MEK is produced in Sf9 cells infected with baculovirus expressing epitope-tagged MEK with a $lysine^{97}$ to alanine mutation (K97A). The epitope sequence Glu-Tyr-Met-Pro-Met-Glu ("Glu-Glu") was fused to the amino-terminus of full-length MEK1.

Anti "Glu-Glu" antibody

A hybridoma cell line expressing an antibody specific for the "Glu-Glu" epitope was obtained from Gernot Walter, UCSD. Cells were grown and antibodies were purified as described (Grussenmeyer et al., Proc. Natl. Acad. Sci. U.S.A., 82, pp. 7952-7954, 1985).

Column buffer

20 mM Tris, pH 8, 100 mM NaCl, 1 mM EDTA, 2.5 mM EGTA, 10 mM $MgCl_2$, 2 mM DTT, 0.4 mM AEBSF, 0.1% n-octyl glucopyranoside, 1 nM okadeic acid, and 10 µg/ml each of benzamidine, leupeptin, pepstatin, and aprotinin (all SIGMA).

2. Add 30 µl of reaction mix containing 10 µl 5x reaction buffer and 0.5 µl 1mM ^{33}P-γ-ATP (20 µCi/ml), 0.5 µl MEK (2.5 mg/ml), 1 µl 50 mM β-mercaptoethanol.

3. Start reaction by addition of 10 µl enzyme dilution buffer containing 1 mM DTT and an empirically determined amount of activated Raf that produces linear incorporation kinetics over the reaction time course.

4. Mix and incubate at room temperature for 90 min.

5. Stop reaction by addition of 50 µl stop solution.

6. Prewet filter plate with 70% ethanol and rinse with water.

7. Transfer 90 µl aliquots of stopped reaction to filter plate.

8. Aspirate and wash four times with 200 µl H_2O.

9. Add 50 µl scintillation cocktail, seal plate, and count in Packard TopCount scintillation counter.

The compound 4-[2-(2-chlorophenyl)-5-(3-hydroxyphenyl)-3H-imidazol-4-yl]pyridine made according to Example 22 above demonstrated an IC_{50} of 5nM.

Map Kinase Phosphorylation assay

Inhibition of Raf kinase activity in intact cells is measured by determining the phosphorylation state of Map Kinase in TPA-stimulated C-33a human epithelial cells. Phosphorylated Map Kinase is detected by "Western" blot using an anti-phospho-Map Kinase antibody.

MATERIALS

C33a Human Epithelial Cells

The C33a cell line is obtained from the ATCC repository, catalog # H TB31, and is maintained in DMEM (Mediatech) + 10 % fetal bovine serum +1% penicillin/streptomycin (Gibco) according to the instructions provided.

3. One hour later, TPA (dissolved in DMSO at 1000x concentratrion) is added at a final concentration of 100 ng/ml.

4. Twenty minutes later, the media is removed from all wells, and 100 µl of boiling hot reducing Laemmli sample buffer is added to each well. The plate is agitated, and the cell lysate is transferred to a 1.5 ml plastic microcentrifuge tube. Each lysate is then sonicated for 10 s, and placed in a boiling water bath for 5-10 minutes. Fifteen microliters of each sample is then loaded on a 10 % Laemmli polyacrylamide gel (Novex), and the gel electrophoresed according to the manufacturer's instructions.

5. Proteins in the gel are electroblotted to a PVDF membrane, which is then rinsed in PBS and blocked with Blocking Buffer for approximately 1 hr at room temperature.

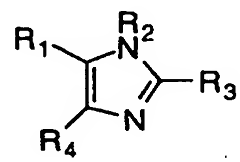
6. The PVDF membrane is rinsed in PBS. The anti-phospho-MapK antibody, diluted approximately 1:500 in antibody dilution buffer, is incubated with the PVDF membrane with gentle agitation overnight at 4 °C.

7. The PVDF membrane is rinsed 3 times for 5 minutes with Blocking Buffer, then incubated with the secondary antibody, diluted approximately 1 : 1000 in antibody dilution buffer, for 1 hr with gentle agitation at room temperature.

8. The PVDF membrane is rinsed 5 times for 5 minutes with Blocking Buffer, then incubated with the chemiluminescent alkaline phosphatase substrate dissolved in Assay Buffer for approximately 5 minutes. The membrane is then rinsed, wrapped in plastic, and exposed to x-ray film to detect blotted proteins.

WHAT IS CLAIMED IS:

1. A method of treating cancer which comprises administering to a mammalian patient in need of such treatment an effective amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,
wherein:

R_1 is 4-pyridyl, pyrimidinyl, quinazolin-4-yl, quinolyl, isoquinolinyl, 1-imidazolyl or 1-benzimidazolyl, which is optionally substituted with one or two substituents each of which is independently selected from C_{1-4} alkyl, halogen, C_{1-4} alkoxy, C_{1-4} alkylthio, $NR_{10}R_{20}$, or N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22};

R_2 is hydrogen, $-(CR_{10}R_{20})_n\ OR_{12}$, heterocyclyl, heterocyclyl C_{1-10} alkyl, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, $(CR_{10}R_{20})_{n'}OR_{13}$, $(CR_{10}R_{20})_{n'}S(O)_mR_{25}$, $(CR_{10}R_{20})_{n'}NHS(O)_2R_{25}$, $(CR_{10}R_{20})_{n'}NR_8R_9$, $(CR_{10}R_{20})_{n'}NO_2$, $(CR_{10}R_{20})_{n'}CH$, $(CR_{10}R_{20})_{n'}SO_2R_{25}$, $(CR_{10}R_{20})_{n'}S(O)_mNR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)NR_{13}OR_{12}$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)NR_{13}or_{12}$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)R_{13}$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}N(OR_{21})C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}N(OR_{21})C(Z)R_{13}$, $(CR_{10}R_{20})_{n'}C(=NOR_{21})R_{13}$, $(CR_{10}R_{20})_{n'}NR_{10}C(=NR_{27})NR_8R_9$, $(CR_{10}R_{20})_{n'}OC(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)OR_{10}$, 5-($R_{25}$)-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroarylalkyl,

$-(CR_{10}R_{20})_{m''}NR_{10}C(Z)R_8$, $-NR_{10}S(O)_{m'}R_{11}$, $-NR_{10}S(O)_{m'}NR_7R_{17}$, $-ZC(Z)R_8$ or $-(CR_{10}R_{20})_{m'''}NR_{16}R_{26}$; wherein m'' is 0 to 5 and m''' is 0 or 1;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties $-SR_5$ being $-SNR_7R_{17}$ and $-SOR_5$ being $-SOH$;

R_6 is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, C_{1-4} alkenyl, C_{2-4} alkynyl or C_{3-5} cycloalkyl,;

R_7 and R_{17} are each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22};

R_8 is hydrogen, heterocyclyl, heterocyclylalkyl or R_{11};

R_9 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R_8 and R_9 may together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12};

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R_{12} is hydrogen, $-C(Z)R_{13}$ or optionally substituted C_{1-4} alkyl, optionally substituted aryl C_{1-4} alkyl, or $S(O)_2R_{25}$;

R_{13} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl or heteroaryl C_{1-10} alkyl;

R_{14} and R_{24} is each independently selected from hydrogen, alkyl, nitro or cyano;

R_{15} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

be optionally substituted with ethoxyalkyl, aminoalkyl, diethylamino, (phenylmethyl-N-methyl)aminoalkyl or (phenylmethyl)amino-1- propyl.

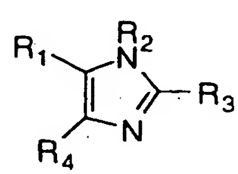
6. A method according to Claim 5 wherein R_2 is 1-formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine or 1-ethoxycarbonyl-4-piperidine.

7. A method according to Claim 1 wherein R_3 is $Q\text{-}(Y_1)_t$; and the group Q comprises an optionally substituted pheny or thienyl moiety.

8. A method according to Claim 7 wherein the substituent Q is phenyl substituted by halogen, halosubstituted alkyl, or $-(CR_{10}R_{20})_nY_2$ and Y_2 is $-OR_8$, $-S(O)'R_{11}$, $-SR_8$, $-S(O)_mNR_8R_9$ or $-NR_8R_9$.

9. A method according to Claim 1 wherein R_4 is optionally substituted phenyl, naphth-1-yl or naphth-2-yl, wherein the phenyl, 4-naphth-1-yl or 5-naphth-2-yl moiety is substituted by one or two substituents each independently selected from halogen, $-SR_5$, $-SOR_5$, $-OR_{36}$, or $-(CR_{10}R_{20})_mNR_{10}R_{20}$, and for other positions of substitution on these rings, the substitution is halogen, $-S(O)_mR_8$, $-OR_8$, $-(CR_{10}R_{20})_mNR_{16}R_{26}$, $-NR_{10}C(Z)R_8$ or $-NR_{10}S(O)_mR_{11}$.

10. A method of treating cancer which comprises administering to a mammalian patient in need of such treatment an effective amount of a compound of formula (I) as represented by the structure:



(I)

or a pharmaceutically acceptable salt thereof.

4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole; and pharmaceutically acceptable salts thereof.

12. A method in accordance with Claim 10 wherein the compound administered is 4-[2-(2-chlorophenyl)-5-(3-hydroxyphenyl)-3H-imidazol-4-yl]pyridine.

13. A method in accordance with claim 1 wherein the compound administered is: 4-(3-hydroxyphenyl)-2-(2-chlorophenyl)-5-(4-pyridyl) imidazole.

14. A method in accordance with claim 1 wherein the compound administered is 4-[2-(2-chlorophenyl)-5-(3-hydroxyphenyl)-3H-imidazol-4-yl]pyridine.

The Patent Office

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Application No: GB 9620892.1
Claims searched: 1 to 14

Examiner: Mr S J Pilling
Date of search: 16 December 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): A5B (BHA, BJA, BJB)

Int Cl (Ed.6): A61K 31/415, 31/44, 31/505, 31/535

Other: ONLINE: CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
A	WO 95/03297 A1 (SMITHKLINE BEECHAM) see the examples.	-

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

wherein:

R_1 is an optionally substituted 4-pyridyl or pyrimidinyl;

R_2 is hydrogen, C_{1-10} alkyl, heterocyclic alkyl, methyl $S(O)_mC_{1-4}$ alkyl;

R_3 is a 2- or 3-thiophene, or a substituted phenyl wherein the substituents are selected from methyl thio, methylsulfinyl, methylsulfonyl, methoxy, N-morpholinomethyl or -C(+NOH)NR_2;

R_4 is phenyl, naphth-1-yl, or naphth-2-yl which is optionally substituted by one or two substituents, each of which is independently selected halogen, $-SR_5$, $-SOR_5$, $-OR_{36}$, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, or $-(CR_{10}R_{20})_mNR_{10}R_{20}$ wherein m is 1 or 2;

R_5 is hydrogen, C_{1-4} alkyl, or NR_7R_{17}, excluding the moieties $-SR_5$ being $-SNR^7R_{17}$ and $-SOR_5$ being -SOH;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{10};

R_{10} is hydrogen or C_{1-4} alkyl;

R_{36} is hydrogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-5} cycloalkyl.

11. A method in accordance with Claim 10 wherein the compound administered is selected from the group consisting of:

4-[2-(2-Chlorophenyl)-5-(3-hydroxyphenyl)-3H-imidazol-4-yl]pyridine;
4-[4-(4-Fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]benzamidoxime;
4-(1-Naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(1-Naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(2-Naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(2-Naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-thiophene)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-thiophene)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;

R_{16} and R_{26} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12};

R_{18} and R_{19} is each independently selected from hydrogen, C_{1-4} alkyl, substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or together denote a oxygen or sulfur;

R_{21} is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R_{22} is R_{10} or $C(Z)$-C_{1-4} alkyl;

R_{23} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-5} cycloalkyl;

R_{36} is hydrogen or R_{23};

R_{25} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10} alkyl, heteroaryl or heteroarylalkyl;

R_{27} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl; or a pharmaceutically acceptable salt thereof.

2. A method according to Claim 1 wherein R_1 is an optionally substituted 4-pyridyl or 4-pyrimidinyl group.

3. A method according to Claim 2 wherein R_1 is an optionally substituted 4-pyridyl or 4-pyrimidinyl group and the optional substituent is selected from alkyl, amino and mono- or di-alkyl amino.

4. A method according to Claim 3 wherein R_2 is an optionally substituted heterocyclic or heterocyclic alkyl moiety.

5. A method according to Claim 2 wherein R_2 is morpholino, pyrrolidinyl, piperidinyl group, piperidinylalkyl, pyrrolidinylalkyl, morpholinoalkyl, and phenoxyalkyl, all of which any

heterocyclyl, or heterocyclyalkyl moieties may be optionally substituted;

n' is an integer having a value of 1 to 10;

m is 0, or the integer 1 or 2;

R_3 is Q-(Y_1)t;

Q is an aryl or heteroaryl group;

t is a number having a value of 1,2, or 3;

Z is oxygen or sulfur;

n is 0 or an integer from 1 to 10;

Y_1 is independently selected from hydrogen, C_{1-5} alkyl, halo-substituted C_{1-5} alkyl, halogen, or -($CR_{10}R_{20}$)nY_2;

Y_2 is -OR_8, -NO_2, -S(O)m'R_{11}, -SR_8, -S(O))m'OR_8, -S(O)mNR_8R_9, -NR_8R_9, -O($CR_{10}R_{20}$)n$NR_8R_9R_9$, -C(O)R_8, -CO_2R_8, -CO_2($CR_{10}R_{20}$)n'CONR_8R_9, -ZC(O)R_8, -CN, -C(Z)NR_8R_9, NR-NR_{10}C(Z)R_8, -C(Z)NR_8OR_9, NR_{10}C(Z)NR_8R_9, -NR_{10}S(O)mR_{11}, -N(OR_{21})C(Z)NR_8R_9, -N(OR_{21})C(Z)R_8, -C(=NOR_{21})R_8, -NR_{10}C(=NR_{15})SR_{11}, -NR_{10}C(=NR_{15})NR_8R_9, -NR_{10}C(=$CR_{14}R_{24}$)SR_{11}, -NR_{10}C(=$CR_{14}R_{24}$)NR_8R_9, -NR_{10}C(O)C(O)NR_8R_9, -NR_{10}C(O)C(O)OR_{10}, -C(-NR_{13})NR_8R_9, -C(=NOR_{13})NR_8R_9, -C(=NOR_{13})ZR_{11}, -OC(Z)NR_8R_9, -NR_{10}S(O)mCR_3, -NR_{10}C(Z)OR_{10}, 5-(R_{18})-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl;

m' is a number having a value of 1 or 2;

R_4 is phenyl, naphth-1-yl or naphth-2-yl which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-1-yl substituent, is halo, cyano,-C(Z)NR_7R_{17}, -C(Z)OR_{23}, -($CR_{10}R_{20}$)m'''$COR_{26}COR_{36}$, SR_5, -SOR_5, OR_{36}, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, -ZC(Z)R_{36}, -NR_{10}C(Z)R_{23}, or -($CR_{10}R_{20}$)m'''$NR_{10}R_{20}$ and which, for other positions or substitution, is halo, cyano, -C(Z)$NR_{16}R_{26}$, -C(Z)OR_8, -($CR_{10}R_{20}$)m'''COR_8, -S(O)mR_8, -OR_8, halo-substituted-C_{1-4} alkyl, C_{1-4}, halo-substituted-C_{1-4} alkyl, - alkyl,

The compound 4-[2-(2-chlorophenyl)-5-(3-hydroxyphenyl)-3H-imidazol-4-yl]pyridine made according to Example 22 above demonstrated an IC_{50} of 0.3 to 1 µM.

Anti-phospho-MAP Kinase antibody

The rabbit polyclonal anti-phospho-MAP kinase antibody is obtained from New England Biolabs (Beverly, MA)

Secondary antibody

The anti-rabbit antibody-alkaline phosphatase conjugate is obtained from New England Biolabs

Acrylamide Gel

Ten percent *bis*-acrylamide electrophoresis gels were obtained from Novex.

Blocking Buffer

1x Phosphate-buffered saline, 0.1 % Tween-20, 5 % nonfat dry milk.

Antibody dilution buffer

1x phosphate-buffered saline, 0.05 % Tween-20, 5 % bovine serum albumin

Alkaline phosphatase substrate

The chemiluminescent alkaline phosphatase substrate, CDP-Star™, is obtained from New England Biolabs.

Assay Buffer

0.1 M diethanolamine, 1 mM $MgCl_2$.

Method

1. C33a cells are grown to confluency in 24 well plates, then starved for 24 hr in DMEM + 0.5 % charcoal-stripped serum.

2. Compound to be tested, dissolved in DMSO at 1000x concentration, is added to each well.

5x reaction buffer

125 mM HEPES pH=8.0, 25 mM $MgCl_2$, 5 mM EDTA, 5 mM Na_3VO_4, 100 µg/ml BSA

Enzyme dilution buffer

25 mM HEPES pH=8.0, 1 mM EDTA, 1 mM Na_3VO_4, 400 µg/ml BSA.

Stop solution

100 mM EDTA, 80 mM sodium pyrophosphate.

Filter plates

Millipore Multiscreen #SE3M078E3, Immobilon-P (PVDF).

METHOD

A. Protein purification

1. Sf9 insect cells were infected with baculovirus and grown as described (Williams et al., Proc. Natl. Acad. Sci. U.S.A., 89, pp. 2922-2926, 1992).

2. All subsequent steps were performed on ice or at 4°C. Cells were pelleted and lysed by sonication in column buffer. Lysates were spun at 17,000x g for 20 min, followed by 0.22 µm filtration.

3. Epitope-tagged proteins were purified by chromatography over a GammaBind Plus (Pharmacia) affinity column to which "Glu-Glu" antibody had been coupled. Proteins were loaded on the column, followed by washes with two column volumes of column buffer, and eluted with 50 µg/ml of peptide antigen (Glu-Tyr-Met-Pro-Met-Glu) in column buffer.

B. Raf kinase assay

1. Add 10 µl of inhibitor or control in 10% DMSO to assay plate.

maintinilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal patents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques.

For the methods of use disclosed herein for the compounds of formula (I), the daily oral dosage regimen will preferably be for about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5 mg to 15 mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 to 15 mg/kg. The dqm about 0.5 to 15 mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those

of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Examplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid, and the like. Examplary of liquid carriers are syrup, peanut oil, olive oil, water, and the like. Similarly, the carrier or diluent may include time delay material well known in the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely, but preferably will be from about 25 mg to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intra-peritoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site, such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from about 0.001% to about 10% w/w, for instance, from 1% to 2% by weight of the formu-

temperature. The reaction mixture was then poured over an ammonium hydroxide (50 mL) and ice mixture. This aqueous layer was extracted with ethyl acetate (3x125 mL) and the organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting oil was chromatographed on silica gel eluting with ethyl acetate to give the imidazole as a foam (2.2 g).

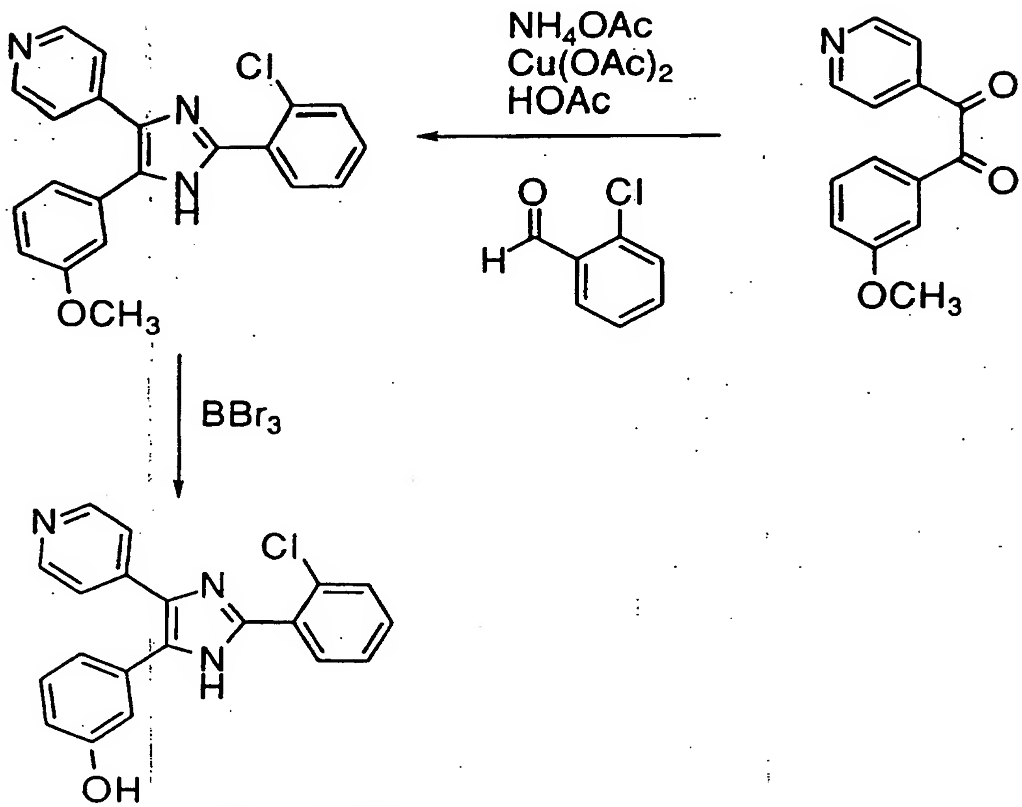
^{1}H NMR (300MHz,CD3OD) δ 8.42 (br s, 2H), 7.83-7.22 (m, 7H), 7.12-6.88 (m, 3H), 3.79 (s, 3H).

STEP D

4-[2-(2-Chlorophenyl)-5-(3-hydroxyphenyl)-3H-imidazol-4-yl]pyridine

To a stirring solution of 4-[2-(2-Chlorophenyl)-5-(3-methoxyphenyl)-3H-imidazol-4-yl]pyridine (1.0 g, 2.8 mmol) in dichloromethane (40 mL) at 0°C was added boron tribromide (8.3 mL of a 1.0 M solution in dichloromethane) dropwise, and the reaction mixture was allowed to warm to ambient temperature. Hydrochloric acid (6 N, 6 mL) was added to the solution which was then heated to 70°C for 20 minutes and then cooled to ambient temperature. The solution was then cooled with ice and basified with aqueous sodium hydroxide (3 N, 12 mL) and the buffered with saturated aqueous sodium hydrogen carbonate (100 mL). The aqueous layer was extracted with ethyl acetate (3x100 mL) and the organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting oil was chromatographed on silica gel eluting with 98:2 to 95:5 dichloromethane:methanol. The resulting solid was crystallized from ethyl acetate to give the phenol as a solid (0.68 g).

^{1}H NMR (300MHz,CD3OD) δ 8.46 (d, J = 4.9 Hz, 2H), 7.82-7.74 (m, 1H), 7.68-7.44 (m, 5H), 7.25-6.91 (m, 2H), 6.87 (d, J = 6.8 Hz, 1H). m.p. = 292-294°C. Anal: Calcd. for $C_{20}H_{14}N_3OCl \cdot 0.30\ H_2O$: C 68.01, H 4.17, N 11.90. Found: C 67.96 H 4.11 N 11.58.



IC_{50} = 5 nM

Step A

1-(3-Methoxyphenyl)-2-pyridin-4-yl-ethane-1,2-diol

To a stirring solution of diisopropylamine (4.5 g, 5.8 mL, 44 mmol) in tetrahydrofuran (170 mL) at -78°C was added n-butyllithium (17.7 mL of a 2.5 M solution in tetrahydrofuran) dropwise. After ten minutes, a solution of 4-pyridylcarbinol *t*-butyldimethylsilyl ether (9.0 g, 40 mmol) in tetrahydrofuran (35 mL) was added dropwise, and the temperature was allowed to rise to -15°C. The solution was again cooled to -78°C and to it was added a solution of 3-anisaldehyde (5.5 g, 4.9 mL, 40 mmol) in tetrahydrofuran (35 mL) dropwise. The solution was allowed to warm to -20°C and was then poured into saturated aqueous sodium hydrogen carbonate (300 mL). The aqueous layer was extracted with ethyl acetate (3x200 mL) and the organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated at

(c) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylsulfonyl) phenyl-5-[4-(2-methylsulfonyl)pyrimidinyl]imidazole

To a solution of 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenyl-5-[4-(2-methylthio)pyrimidinyl]imidazole (0.10 g, 0.24 mmol) in dichloromethane (10 mL) is added 80% m-chloroperbenzoic acid (0.25 g, 1.2 mmol). After stirring at ambient temperature for 18 hours, the reaction mixture is poured into saturated aqueous sodium carbonate and the layers are separated. The organic phase is washed with saturated aqueous sodium chloride, dried (MgSO4) and evaporated. The residue is purified by flash chromatography eluting successively with dichloromethane and 1% methanol in dichloromethane to afford the the title compound (0.11 g).

(d) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenyl-5-[4-(2-amino)pyrimidinyl]imidazole

4-(4-Fluoro)phenyl-1-methyl-2-(4-methylsulfonyl)-phenyl-5-[4-(2-methylsulfonyl)pyrimidinyl]imidazole (0.50 g, 0.10 mmol) is added to concentrated ammonium hydroxide (2 mL) and reaction mixture is heated to 150°C in a sealed vessel. After cooling to ambient temperature, the reaction mixture is diluted with water, extracted twice with dichloromethane and once with 4% methanol in dichloromethane. The organic layers are combined and the solvent evaporated. The residue is purified by flash chromatography eluting successively with 2%, 4% and 10% methanol in dichloromethane followed by trituration with ether to afford the title compound.

EXAMPLE 22

4-[2-(2-Chlorophenyl)-5-(3-hydroxyphenyl)-3H-imidazol-4-yl]pyridine

chromatography, eluting with 9:1 CHCl3/MeOH, followed by 90:10:1 CHCl3/MeOH/NH3. The material is triturated with Et2O to afford the title compound (1.5 g).

EXAMPLE 19

2-(4-Biotinamidomethylphenyl)-1-methyl-4-phenyl-5-(4-pyridyl)-imidazole

To a solution contained 2-(4-Aminomethylphenyl)-4-phenyl-5-(4-pyridyl)-imidazole (1 equivalent) in DMF is added N-hydroxysuccinimide biotin (1.2 eq). Following normal workup and chromatography the title compound is obtained.

EXAMPLE 20

4-(4-Fluorophenyl)-1-methyl-2-(4-methylsulfinyl) phenyl-5-(4-pyridyl)imidazole

(a) N-Methyl-4-(methylthio)phenyl benzamidine
The title compound is prepared following the procedure for Garigipati (Tetrahedron Lett., 1990, 31 (14), 1969) except using methylamine hydrochloride and 4-(methylthio)benzonitrile.

(b) 4-4(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenylimidazole
The title compound is prepared following the procedure of Fitzi (U.S. Patent 3,940,486) except using N-methyl-4-(methylthio)phenylbenzamidine and 2-chloro-4'-fluoroacetophenone.

(c) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio) phenyl-5-(4-pyridyl)imidazole
The title compound is prepared by the procedure of Lantos, et al. (J. Org. Chem., 1988, 53, 4223) except using 4-(4-fluoro)phenyl-1-methyl-2-(4-methylthio)phenylimidazole.

The title compound is prepared using the same procedure as described in Example 2, except using 4-(4-Fluorophenyl)-2-(2-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole.

EXAMPLE 11

4-(4-Fluorophenyl)-2-(thiophen-2-yl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 2(b), except using 2-thiophene carboxaldehyde.

EXAMPLE 12

4-(4-Fluorophenyl)-2(thiophen-3-yl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 81(b), except using 3-thiophene carboxaldehyde.

EXAMPLE 13

4-(naphth-1-yl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 2(a), except using 1-naphth-(N-methoxy-N-methyl)amide.

EXAMPLE 14

4-(naphth-2-yl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 2(a), except using 2-naphth-(N-methoxy-N-methyl)amide.

collected by filtration to afford the title compound (0.65 g), which is recrystallized from MeOH.

EXAMPLE 4

4-(4-Fluoropheny)-2-(4-methylsulfonylphenyl)-5-(4-pyridyl)-1H-imidazole

To a solution of 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole (3.7 g, 9.8 mmol) [See Ex. 3 above.] in 1:10 3N HCl/H_2O (88 mL) is added a solution of $KMnO_4$ (1.5 g, 9.8 mmol) in H_2O (15 mL0. After stirring at rt for 1 hour, additional $KMnO_4$ (0.15 g, 0.9 mmol) is added, and stirring is continued for 15 minutes. The mixture is then poured into saturated aqueous Na_2SO_3 (200 mL), and the pH is adjusted to slightly acidic by the addition of 3 N HCl, then to neutral by the addition of 2.5 N NaOH. The solid which forms is collected by filtration, washed successively with H_2O and MeOH and recrystallized three times from MeOH to afford the title compound (0.63 g).

EXAMPLE 5

4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

The title compound is prepared using the same procedure as described in Example 2(b), except using 3-(methylthio)-benzaldehyde.

EXAMPLE 6

4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole

EXAMPLE 1

2-(4-Cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole

(a) To a solution of 2-(4-cyanophenyl)-4-(4-fluorophenyl)-N-1-hydroxy-5-(4-pyridyl)imidazole (4.5 g, 13.2 mmol) [See 1(b) below.] in DMF (50 mL) is added triethyl phosphite (3.4 mL, 20 mmol), and the resulting mixture is heated at 100°C for 2 hours. After cooling, the mixture is poured into H_2O, and the solid is collected by filtration, washed with H_2O and dried *in vacuo* to afford the title compound (4.0 g)

(b) 2-(4-Cyanophenyl)-4-(4-fluorophenyl)-N-1-hydroxy-5-(4-pyridyl)imidazole

The title compound is prepared using the same procedure (U.S. 3,940,486) employed to prepare 2-(t-butyl)-4-(phenyl)-N-1-hydroxy-5-(4-pyridyl)imidazole, except using 4-fluoro-2-hydroxyimino-2-(4-pyridyl)acetophenone and 4-cyanobenzaldehyde.

EXAMPLE 2

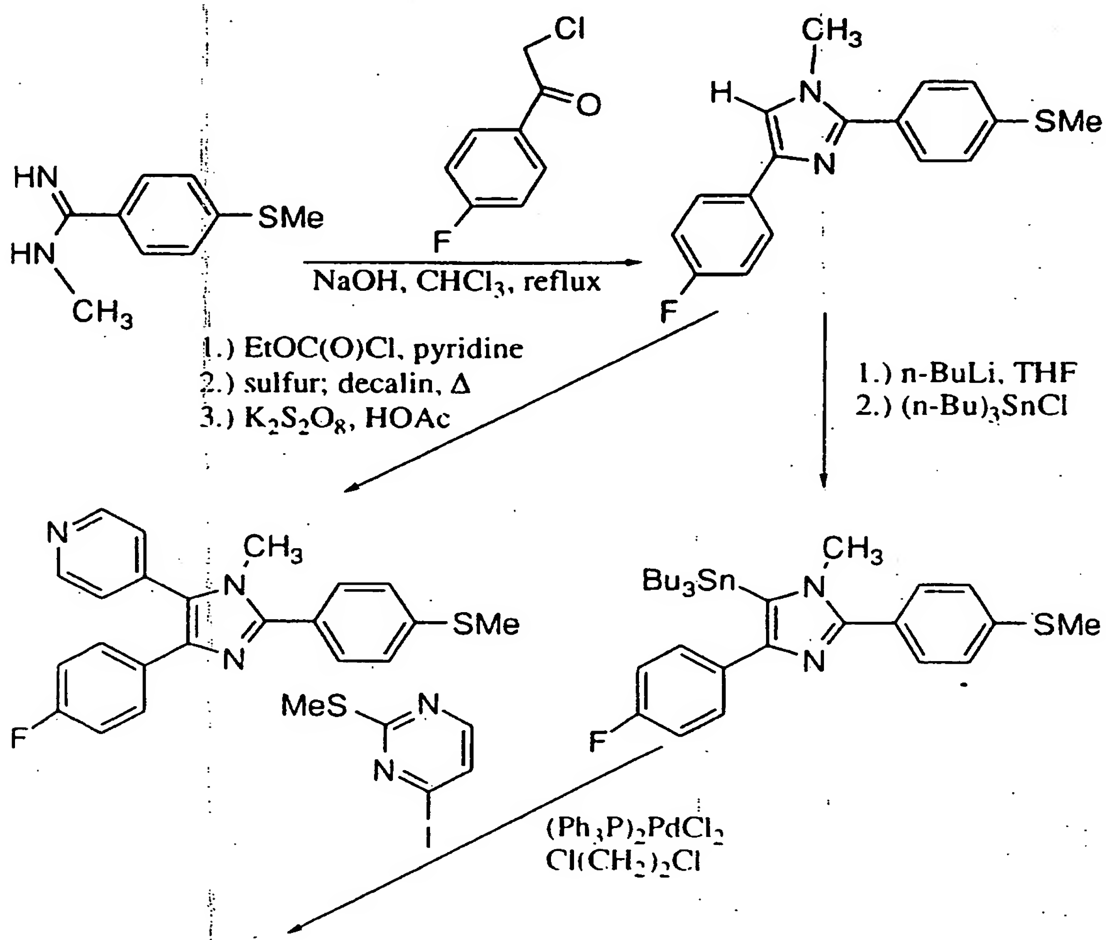
4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

(a) 1-(t-Butyldimethylsilyloxy)-2-(4-fluorophenyl)-1-(4-pyridyl)ethanone

To a -20°C solution of diisopropylamine (64.4 mL, 0.46 mol) and THF (120 mL) is added 207.8 mL (0.52 mol, 2.5 M solution in hexanes) of n-butyllithium dropwise over 15 min. The temperature is lowered to -15°C and the mixture is stirred for 0.5 hours. The solution is cooled to -20°C and 98.14 g (0.44 mol) of 4-(t-butyldimethylsilyloxy)methyl pyridine is added dropwise over 20 minutes. After stirring at -20°C for 45 minutes, a solution of 4-fluoro-N-methoxy-N-methylbenzamide (84.5 g, 0.46 mol) [See Ex. 10, step (a).] in THF (90 mL) is added dropwise over 0.5 hours. Once the addition is complete, the ice bath is removed and the reaction mixture is warmed to 0°C for 1 hour, then stirred at rt

N-1 product has to be separated from the mixture of N-1 and N-3 products, for instance by chromatography or fractional crystallization.

Compounds of Formula (I) wherein R2 is methyl and R1 is 4-pyridyl or 4-(2-amino)pyrimidinyl for example may be made by the route indicated below.



Compounds of formula (XI) are imidazoles and may be obtained by any of the procedures herein before described for preparing compounds of formula (I). In particular, an α-halo-ketone R_4COCH_2Hal (for compounds of formula (XI) in which T_1 is hydrogen) or R_1COCH_2Hal (for compounds of formula (XI) in which T_4 is hydrogen) may be reacted with an amidine of formula (IV) or a salt thereof, in an inert solvent such as a halogenated hydrocarbon solvent, for instance chloroform, at a moderately elevated temperature, and, if necessary, in the presence of a suitable condensation agent such as a base. The preparation of suitable α-halo-ketones is described in WO 91/19497. For a compound of formula (XI) in which T_3 is hydrogen, an α-diketone of formula (II) may be condensed with a formaldehyde or an equivalent thereof, in the presence of a source of ammonia. Suitable bromo derivatives of the compound of formula (XI) may be obtained by brominating the corresponding compound of formula (XI) under standard brominating conditions, for instance bromine in a solvent such as dichloromethane or THF.

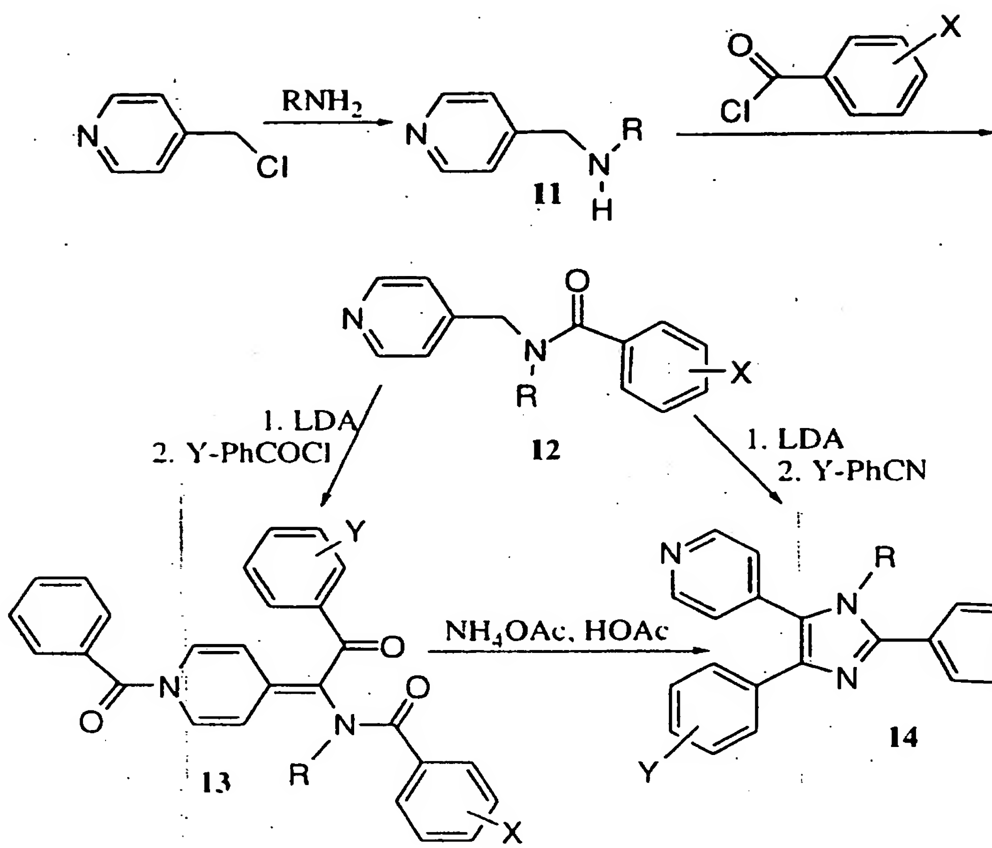
Compounds of formula (I) may also be prepared by a process which comprises reacting a compound of formula (XI), wherein T_1 is hydrogen, with an N-acyl heteroaryl salt, according to the method disclosed in U.S. Patents 4,803,279, 4,719,218 and 5,002,942, to give an intermediate in which the heteroaryl ring is attached to the imidazole nucleus and is present as a 1,4-dihydro derivative thereof, which intermediate may then be subjected to oxidative-deacylation conditions. The heteroaryl salt, for instance a pyridinium salt, may be either preformed or, more preferably, prepared *in situ* by adding a substituted carbonyl halide (such as an acyl halide, aroyl halide, an arylalkyl haloformate ester, or, preferably, an alkyl haloformate ester, such as acetyl bromide, benzoylchloride, benzyl chloroformate, or, preferably, ethyl chloroformate) to a solution of the compound of formula (XI) in the heteroaryl compound R_1H or in an inert solvent such as methylene chloride to which the heteroaryl compound has been added. Suitable deacylating and oxidizing conditions as described in U.S. Patent Nos. 4,803,279, 4,719,218 and 5,002,942. Suitable oxidizing systems include sulfur in an inert solvent

boromo, iodo, fluorosulfonate and trifluoromethanesulphonate derivatives. Suitable procedures are described in WO/91/19497, the disclosure of which is herewith incorporated by reference.

Suitable organomagnesium and organozinc derivatives of a compound of formula (XI) may be reacted with a halogen, fluorosulfonate or triflate derivative of the hereroaryl or aryl ring, in the presence of a ring coupling catalyst, such as a palladium (O) or palladium (II) catalyst, following the procedure of Kumada, et al., Tetrahedron Letters, **22**, 5319 (1981). Suitable such catalysts include *tetrakis* (triphenylphosphine)palladium and $PdCl_2$[1,4-*bis*-(diphenylphosphino)-butane], optionally in the presence of lithium chloride and a base, such as triethylamine. In addition, a nickel (II) catalyst, such as Ni(II)Cl_2(1,2-biphenylphosphino)ethane, may also be used for coupling an aryl ring, following the procedure of Pridgen, J. Org. Chem, 1982, **47**, 4319. Suitable reaction solvents include hexamethylphosphoramide. When the heteroaryl ring is 4-pyridyl, suitable derivatives include 4-bromo- and 4-iodo-pyridine and the fluorosulfonate and triflate esters of 4-hydroxy pyridine. Similarly, suitable organomagnesium and organozinc derivatives may be obtained by treating a compound of formula (XI) or the bromo derivative thereof with an alkyllithium compound to yield the corresponding lithium reagent by deprotonation or transmetallation, respectively. This lithium intermediate may then be treated with an excess of a magnesium halide or zinc halide to yield the corresponding organometallic reagent.

A trialkyltin derivative of the compound of formula (XI) may be treated with a bromide, fluorosulfonate, triflate, or, preferably, iodide derivative of an aryl or heteroaryl ring compound, in an inert solvent such as tetrahydrofuran, preferably containing 10% hexamethyl-phosphoramide, in the presence of a suitable coupling catalyst, such as a palladium (O) catalyst, for instance *tetrakis*-(triphenylphosphine)-palladium, by the method described in by Stille, J. Amer. Chem. Soc., 1987, **109**, 5478, US Patents 4,719,218 and 5,002,942, or by using a palladium (II) catalyst in the presence of lithium chloride optionally with an added base such as triethylamine, in an inert solvent such as dimethyl

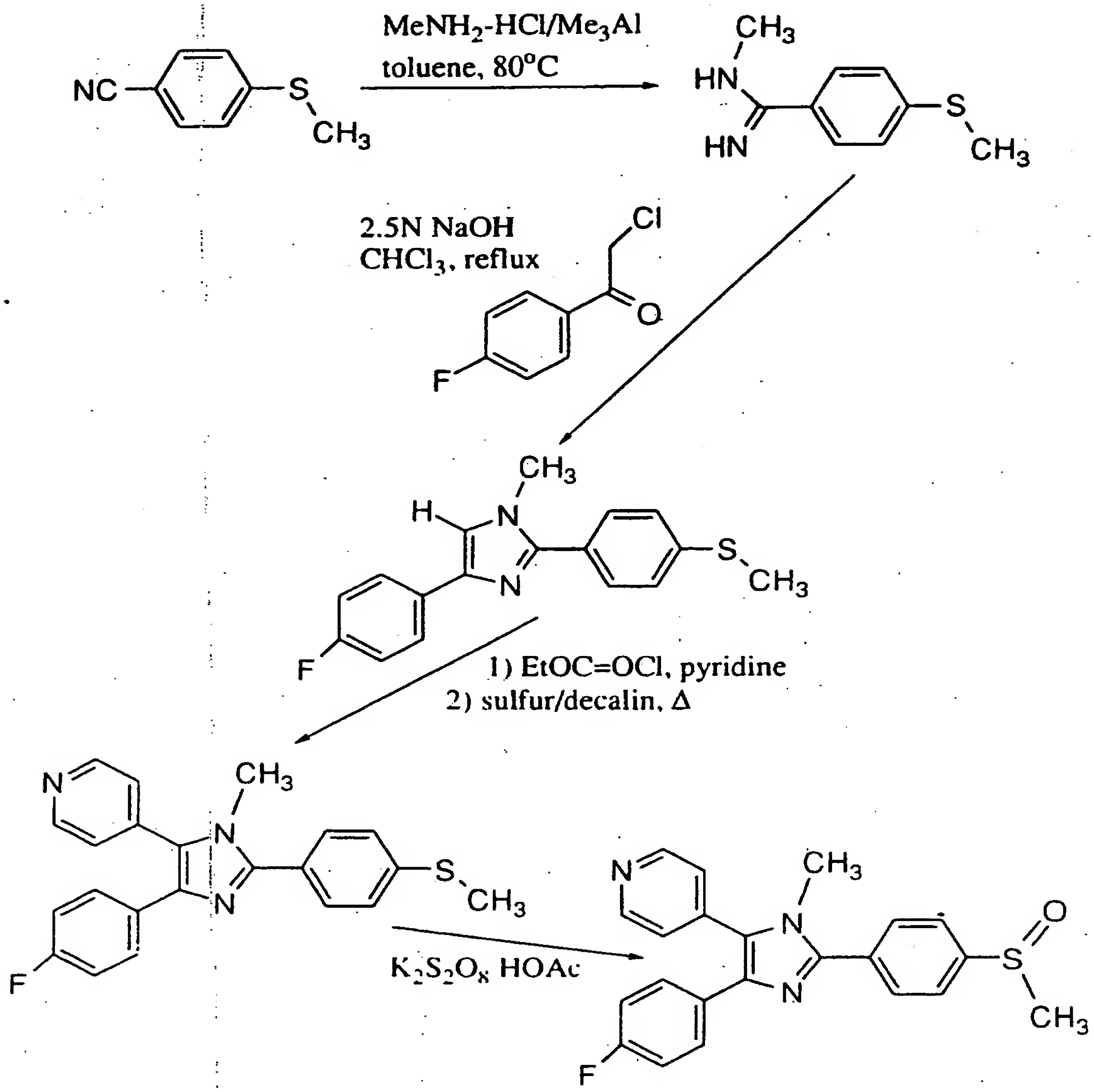
SCHEME III



In a further process, compounds of formula (I) may be prepared by treating a compound of formula (X):

$$R'COCHR''X_cCOR_3 \qquad (X)$$

wherein R', R'' and R_3 are as hereinbefore defined and X_c is O or NH, with a source of ammonia, as hereinbefore described, under imidazole ring forming conditions or cyclizing the corresponding Schiff's base, formed by treating the compound of formula (X) in which X_c is NH with an amine R_2NH_2, for instance thermally or with the aid of a cyclizing agent such as phosphorus oxychloride or phosphorus pentachloride (see Engle and Steglich, Liebigs Ann Chem, 1978, 1916 and Strzybny, et al., J. Org. Chem, 1963, **28**, 3381). Compounds of formula (X) may be obtained, for instance, by acylating the corresponding α-keto-oxime (X_c is NH) or α-hydroxyketone (X_c is O) with an acyl halide of the formula



In a further process, a compound of formula (I) may be obtained by treating an iminoether of formula (V):

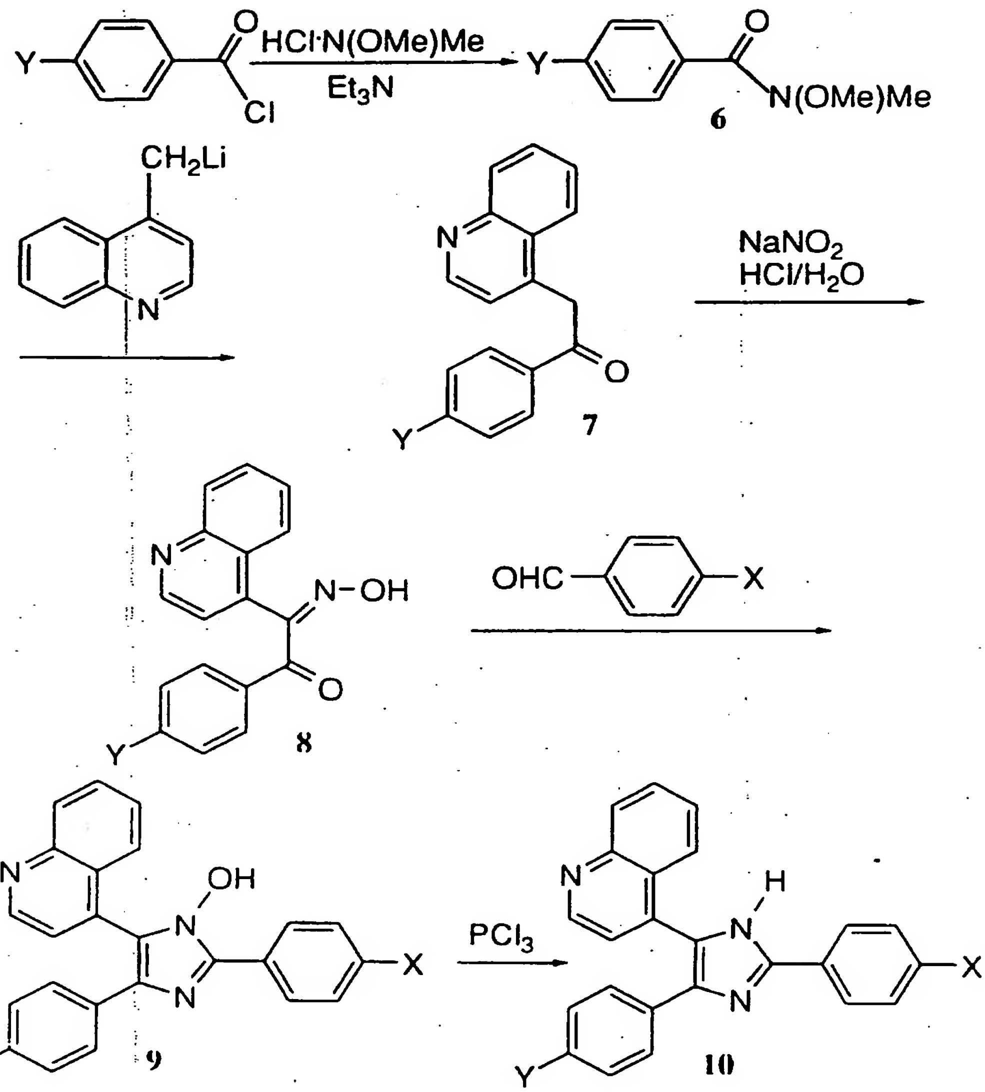
$R_3C{=}NOR$ (V)

wherein R_3 is as hereinbefore defined and R is C_{1-10} alkyl, aryl or aryl C_{1-4} alkyl, with an α–aminoketone of the formula (VI):

$R'CH_2NHCOR''$ (VI)

wherein one of R' and R" is R_1 and the other is R_4 in a suitable solvent.

SCHEME II

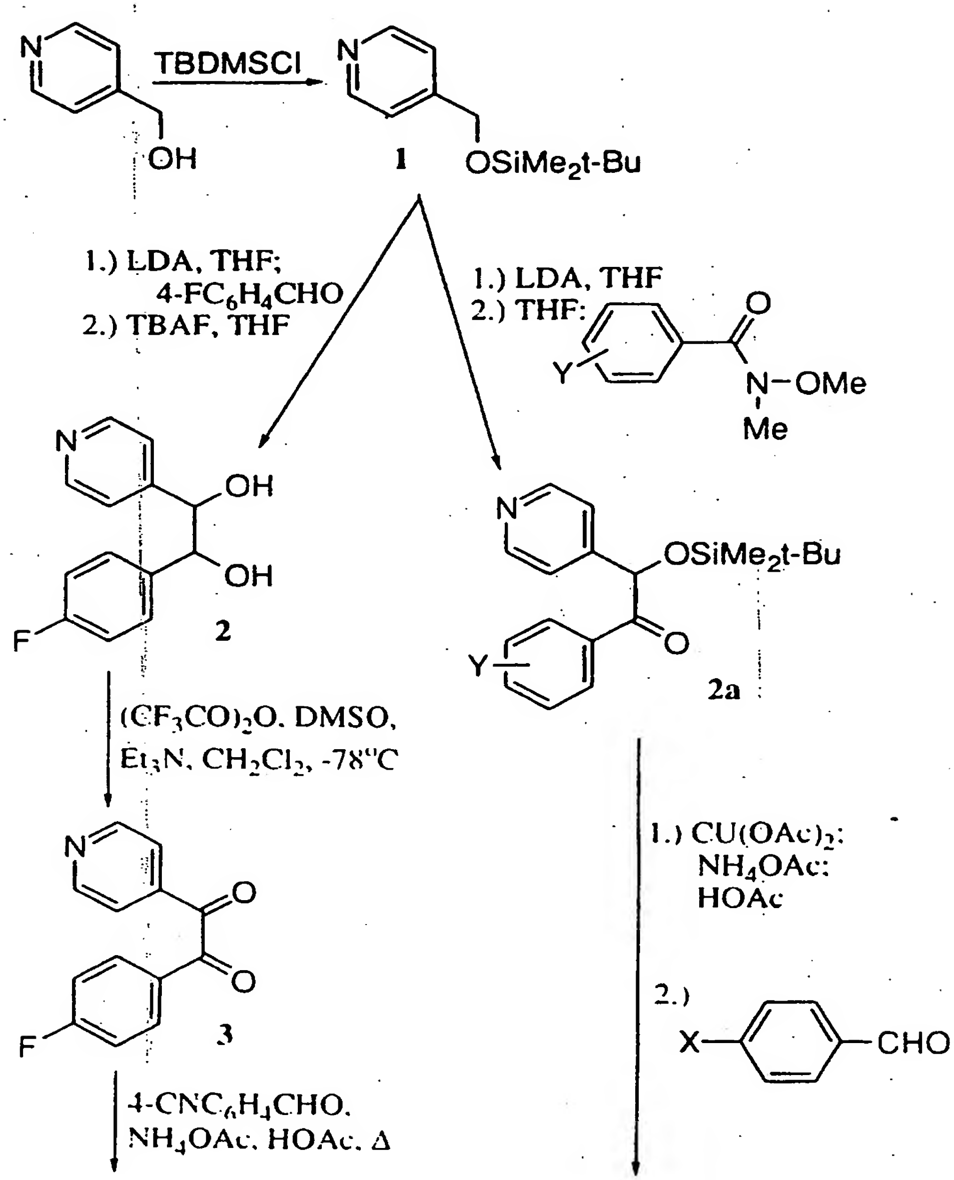


In a further process, a compound of formula (I) may be obtained by treating an α-hydroxyketone compound of formula (IIA):

R'CHOHCOR" (IIA)

wherein one of R' and R" is R_1 and the other is R_4, a suitably protected derivative thereof or the α-hydroxy-oxime or α-haloketone derivative thereof, with an oxidizing agent capable of converting said compound into the corresponding α-diketone, in the presence of an aldehyde of

SCHEME I



TBDMSCl
OH
1
OSiMe2t-Bu
1.) LDA, THF;
4-FC6H4CHO
2.) TBAF, THF
1.) LDA, THF
2.) THF:
O
Y
N-OMe
Me
N
OH
OH
F
2
OSiMe2t-Bu
O
2a
(CF3CO)2O, DMSO,
Et3N, CH2Cl2, -78°C
1.) CU(OAc)2;
NH4OAc;
HOAc
2.)
X
CHO
3
4-CNC6H4CHO,
NH4OAc, HOAc, Δ

under reflux conditions, and, if desired, in a sealed vessel optionally under pressure and/or an inert gas atmosphere, for instance nitrogen.

A further suitable source of ammonia is hydroxylamine, in which case the initially formed imidazole is an N-hydroxy-N-oxide imidazole. This may then be reduced to the corresponding N-hydroxy imidazole by treating with a suitable reducing agent such as sodium borohydride, in an appropriate solvent such as methanol, following the method of Akange and Allan, Chem and Ind, 5, Jan 1975, 28. The N-hydroxy imidazole may in turn be converted to an imidazole of formula (I) in which R_2 is hydrogen by treatment with a conventional deoxygenating agent such as phosphorus trichloride as a trialkylphosphite such as trimethyl- or triethyl-phosphite. N-hydroxy-N-oxide imidazoles may be readily obtained by treating an α-diketone of formula (II) with an aldehyde of formula (II) with about two equivalents of hydroxylamine or the corresponding aldoxime and about one equivalent of hydroxylamine, under proton catalysis. Alternatively, the N-oxide may be obtained by the acid catalyzed condensation of the corresponding α-dioxime or α-keto-oxime with an aldoxime of the aldehyde of formula (III).

When the compound of formula (II) is an α-keto-oxime derivative, it will be appreciated that the product initially obtained will be a compound of formula (I) in which R2 is hydroxyl which may be converted into a compound of formula (I) in which R2 is hydrogen as described above.

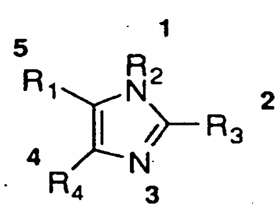
It will be appreciated by those skilled in the art that, in some instances, it will not be necessary to provide a separate source of ammonia as the α-diketone or aldehyde equivalent may already contain such a source. Examples of this include α-dioxime or α-keto-oxime and aldoxime.

The compounds of formula (II) may be obtained by applying well-known synthetic procedures, some of which are illustrated in schemes I and II. Although these illustrate syntheses in which R_4 is either 4-pyridyl or 4-quinolinyl, they may be equally applied to any of the other heteroaryl rings within the definition of R_4 by appropriate choice of starting material.

to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent Y_1 in R_3 comprises a carboxy group. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

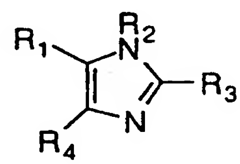
For the purposes herein of nomenclature, the compounds of formula (I) are named by their position corresponding to:



Compounds of formula (I) are imidazole derivatives which may be readily prepared using procedures well-known to those skilled in the art, and described in, for instance, Comprehensive Heterocyclic Chemistry, ed Katritzky and Rees, Pergamon Press, 1984, 5, 457-497, from starting materials which are either commercially available or can be prepared from such by analogy with well-known processes. A key step in many such syntheses is the formation of the central imidazole nucleus, to give compounds of formula (I). Suitable procedures are described in *inter alia* U.S. Patent Nos. 3,707,475 and 3,940,486 and in PCT Appli-

$-(CR_{10}R_{20})_mNR_{10}R_{20}$, and for other positions of substitution on these rings the substitution is halogen, $-S(O)_mR_8$, $-OR_8$, $-(CR_{10}R_{20})_mNR_{16}R_{26}$, $-NR_{10}C(Z)R_8$ and $-NR_{10}S(O)_mR_{11}$.

Another embodiment of the invention is a method of treating cancer which comprises administering to a mammalian patient in need of such treatment an effective amount of a compound of formula (I), as represented by the structure:



(I)

or a pharmaceutically acceptable salt thereof,
wherein:
R_1 is an optionally substituted 4-pyridyl or pyrimidinyl;
R_2 is hydrogen, C_{1-10} alkyl, heterocyclic alkyl, methyl $S(O)_mC_{1-4}$ alkyl;
R_3 is a 2- or 3-thiophene, or a substituted phenyl wherein the substituents are selected from methyl thio, methylsulfinyl, methylsulfonyl, methoxy, N-morpholinomethyl or $-C(+NOH)NR_2$;
R_4 is phenyl, naphth-1-yl, or naphth-2-yl which is optionally substituted by one or two substituents, each of which is independently selected halogen, $-SR_5$, $-SOR_5$, $-OR_{36}$, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, or $-(CR_{10}R_{20})_mNR_{10}R_{20}$ wherein m is 1 or 2;
R_5 is hydrogen, C_{1-4} alkyl, or NR_7R_{17}, excluding the moieties $-SR_5$ being $-SNR^7R_{17}$ and $-SOR_5$ being $-SOH$;
R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{10};
R_{10} is hydrogen or C_{1-4} alkyl;

4-(1-Naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(1-Naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(2-Naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(2-Naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-thiophene)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-thiophene)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-1-methyl-5-(4-pyridyl) imidazole;
4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-1-(N-morpholino-propyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-1-(methylthio-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-1-(methylsulfinyl-1-propyl)-2-([4-N-morpholino-methyl]phenyl)-5-(4-pyridyl)imidazole; and
4-(4-Fluorophenyl)-1-(methylsulfonyl-1-propyl)-2-([4-N-morpholino-methyl]phenyl)-5-(4-pyridyl)imidazole.

Consequently, one embodiment of the invention is a method of treating cancer as described above wherein R_1 is an optionally substituted 4-pyridyl or 4-pyrimidinyl group.

A further embodiment of the invention is a method of treating cancer as described above wherein R_1 is an optionally substituted

Preferred substituents for use in R_3 when the aryl or heteroaryl group Q is disubstituted include those hereinbefore listed for use when Q is mono-substituted and, as further substituent(s), halogen and C_{1-10} alkyl. When R_3 is phenyl substituted with two or three substituents, the alkyl moieties preferably have from one to three carbons, more preferably one. Preferred ring positions for two substituents are the 3- and 4-positions and, for three substituents, the 3-, 4- and 5-positions. The substituents at the 3- and 5-positions are preferably C_{1-2} alkyl, such as methyl, or halogen, such as bromo, fluoro or chloro, while the substituent at the 4-position is preferably hydroxyl.

More preferably, for R_3 substituents wherein Y_1 is $(CR_{10}R_{20})_nY_2$, n is 0 or 1 and Y_2 is -OH, $-S(O)_{m'}R_{11}$, especially where R_{11} is C_{1-10} alkyl; $-SR_8$, especially where R_8 is C_{1-10} alkyl; $-NR_8R_9$, especially where R_8 and R_9 are hydrogen, alkyl, aryl alkyl, or aryl or R_8 and R_9 together with the nitrogen to which they are attached form a pyrrolidinyl, piperidinyl or morpholinyl ring, more preferably the R_8 and R_9 terms in the NR_8R_9 moiety are hydrogen, methyl or benzyl; $-CO_2R_8$, especially where R_8 is hydrogen or C_{1-10} alkyl; $-S(O)_{m'}NR_8R_9$, especially where R_8 and R_9 are each hydrogen or C_{1-10} alkyl: $-NR_{10}S(O)_mR_{11}$, especially where R_{10} is hydrogen and R_{11} is C_{1-10} alkyl or 5-(R_{18}(-1,2,4-oxadiazol-3-yl and 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl, especially where R_{12} is hydrogen and R_{18} and R_{19} are hydrogen or C_{1-10} alkyl, or together are oxo.

More preferably, Y_1 is methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, N,N-dimethylaminomethyl, N-benzyl-N-methylaminomethyl, N-morpholinomethyl, methanesulfonamido, sulphonamidomethyl, 5-methyl-4,5-dihydro-1,2,4-oxadiazol-3-yl or 5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl.

In Formula (I), suitably R4 is a halo-substituted phenyl, naphth-1-yl, or naphth-2-yl ring. Preferably R4 is a halo-substituted phenyl, and preferably the halogen is fluorine, more preferably in the 4-position.

A preferred grouping of formula (I) includes compounds wherein R_2 is an optionally substituted C_{1-10} alkyl, optionally

(wherein t is 0, or an integer of 1 to 4), $(CR_{10}R_{20})_t\ NR_{10}R_{20}$, especially amino or mono-or di-alkylamino; $(CR_{10}R_{20})_tS(O)_mR_{25}$, wherein m is 0, 1 or 2; -SH-, $-(CR_{10}R_{20})_n-NR_8R_9$, $-NR_{10}C(Z)R_8$ (such as $-NHCO(C_{1-10}$ alkyl)); $-NR_{10}S(O)_mR_{25}$ (such as $-NHSO_2(C_{1-10}$alkyl). Preferably the phenyl is substituted in the 3 or 4-position by $-(CR_{10}R_{20})_tS(O)_mR_{25}$ and R_{25} is preferably C_{1-10} alkyl, especially methyl.

When R_2 is an optionally substituted heteroaryl or heteroarylalkyl group, the ring may be optionally substituted one or more times, preferably by one or two substituents, independently selected from C_{1-4} alkyl, halogen, especially fluoro or chloro. $(CR_{10}R_{20})_tOR_{13}$, $-(CR_{10}R_{20})_tNR_{10}R_{20}$, especially amino or mono- or di-alkylamino - $(CR_{10}R_{20})_tS(O)_mR_{25}$, wherein m is 0, 1 or 2; -SH, $-(CR_{10}R_{20})_n-NR_8R_9$, $-NR_{10}C(Z)R_8$ (such as $-NHCO(C_{1-10}$ alkyl)); $-NR_{10}S(O)_mR_{25}$ (such as $-NHSO_2(C_{1-10}$ alkyl)); t is 0, or an integer of 1 to 4.

One skilled in the art would readily recognize that, when R_2 is a $(CR_{10}R_{20})_{n'}OC(Z)R_{13}$, or $(CR_{10}R_{20})_{n'}OC(Z)NR_8R_9$ moiety, or any similarly substituted group that n' is preferably at least 2 which will allow for the synthesis of stable compounds.

Suitably, R_3 is $Q-(Y_1)_t$; and Q is an aryl or heteroaryl group. Preferably when Q is a heteroaryl moiety, it is a 2- or 3-thiophene. Preferably R_3 is a substituted phenyl. More preferred Q is phenyl. Q is independently substituted 1 to 3 times by Y_1. Preferably t is 1 or 2. More preferably, when R_3 is mono-substituted phenyl, the substituent is located at the 4-position.

Preferably Q is substituted by 1 or 2 substituents which include halogen, C_{1-5} alkyl and $-(CR_{10}R_{20})_nY_2$ wherein Y_2 is $-OR_8$, $-NO_2$, $-S(O)_{m'}R_{11}$, $-SR_8$, $-S(O)_mNR_8R_9$; $-NR_8R_9$, $-O(CR_{10}R_{20})_nNR_8R_9$, $-C(O)R_8$, $-CO_2R_8$, $-CO_2(CR_{10}R_{20})_{n'}COMR_8R_9$, -CN; $-C(Z)NR_8R_9$, $-NR_{10}S(O)_mR_{11}$, $-NR_{10}C(Z)R_8$, $-NR_{10}C(Z)NR_8R_9$, $-C(Z)NR_8OR_9$, $-N(OR_{21})C(Z)NR_8R_9$, $-NR_{10}C(=NR_{15})NR_8R_9$, $-C(=NOR_{13})NR_8R_9$,

the free nitrogen, such as in the piperidinyl group or pyrrole ring, or on the ring itself. Preferably the ring is a piperidine or pyrrole, more preferably piperidine. The heterocyclyl ring may be optionally substituted one to four times independently by the same substituents noted above for the heterocyclic alkyl groups.

Preferably, if the ring is a piperidine, the ring is attached to the imidazole at the 4-position, and the substituents are directly on the available nitrogen, i.e., a 1-formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, 1-ethoxycarbonyl-4-piperidine. If the ring is substituted by an alkyl group and the ring is attached in the 4-position, it is preferably substituted in the 2 or 6 position or both, such as 2,2,6,6,-tetramethyl-4-piperidine. Similarly, if the ring is a pyrrole, the ring is attached to the imidazole at the 3-position, and the substituents are aldo directly on the available nitrogen. The substitution on the heterocyclic ring is preferably the same regardless if it is a heterocyclic or heterocyclic alkyl moiety.

When R_2 is an optionally substituted C_{3-7} cycloalkyl, or an optionally substituted C_{3-7} cycloalkyl C_{1-10} alkyl, the cycloalkyl group is preferably a C_5 to C_6 ring, which ring may be optionally substituted one or more times independently by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; C_{1-10} alkoxy, such as methoxy or ethoxy; $S(O)_m$ alkyl, wherein m is 0, 1, or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono and di-substituted amino, such as in the NR_7R_{17} group, or where the R_7R_{17} may cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C_{1-10} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halo-substituted alkyl, such as CF_3; hydroxy substituted C_{1-10} alkyl; $C(O)OR_{13}$, such as the free acid or methyl ester derivative; an optionally substituted aryl, such as phenyl; an optionally substituted arylalkyl, such as benzyl or phenethyl; and further where these aryl moieties may also be substituted one to two times by halogen; hydroxy; C_{1-10} alkoxy; $S(O)_m$ alkyl; amino, mono and di-substituted amino, such as in the NR_7R_{17} group; alkyl or halo-substituted alkyl.

or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono and di-substituted amino, such as in the NR_7R_{17} group; or where the R_7R_{17} may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C_{1-10} alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc., or cyclopropyl methyl; halo-substituted C_{1-10} alkyl, such CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may also be substituted one or two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_m$alkyl, amino, mono and di-substituted amino, such as in the NR_7R_{17} group, C_{1-10} alkyl, or CF_3.

In Formula (I), preferred R_1 moieties are 4-pyrimidinyl, 4-pyridyl or 4-quinolyl groups of which the 4-pyrimidinyl and the 4-pyridyl are preferred. These groups are preferably substituted with a C_{1-4} alkyl, in particular methyl, or a $NR_{10}R_{20}$ group, preferably where R_{10} and R_{20} are both hydrogen. More preferred is the 4-pyridyl derivative substituted at the 2-position with a C_{1-4} alkyl, especially 2-methyl-4-pyridyl, or the 4-pyrimidinyl derivative substituted at the 2-position with C_{1-4} alkyl or $NR_{10}R_{20}$, more preferably with $NR_{10}R_{20}$, and R_{10} and R_{20} are preferably hydrogen.

In Formula (I), R_2 is preferably an optionally substituted C_{1-10} alkyl, an optionally substituted aryl, an optionally substituted heterocyclic alkyl or an optionally substituted heterocyclic ring. The alkyl chain, while being of 1 to 10 carbons in length, is preferably from 2 to 4 carbons, more preferably 3 in length. The alkyl chain is preferably substituted by an aryl, heteroaryl or heterocyclic moiety, or the alkyl chain is interrupted by an oxygen $[(CR_{10}R_{20})_{n'}OR_{13}]$ or sulfur group $[(CR_{10}R_{20})_{n'}S(O)_mR_{25}]$ (which may be optionally oxidized) or by an optionally substituted amine derivative $[(CR_{10}R_{20})_{n'}NR_8R_9]$. Other substituted alkyl groups include $(CR_{10}R_{20})_{n'}(Z)OR_{13}$, $(CR_{10}R_{20})_{n'}NHS(O)_2R_{25}$, $(CR_{10}R_{20})_{n'}C(Z)R_{13}$ or $(CR_{10}R_{20})_{n'}C(=NOR_{21})R_{13}$. R_2 may also be hydrogen when R_4 is not an unsubstituted pyridyl and R_3 a substituted phenyl.

DETAILED DESCRIPTION OF THE INVENTION

The following terms, as used herein, refer to:

"halo" - all halogens, that is chloro, fluoro, bromo and iodo;

"C_{1-10} alkyl" or alkyl" - both straight and branched chain radicals of 1-10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl and the like;

"aryl" - phenyl and naphthyl;

"heteroaryl" (on its own or in any combination, such as "heteroaryloxy")- a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited to pyrrole, quinoline, isoquinoline, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole or benzimidazole;

"heterocyclic" (on its own or in any combination, such as "heterocyclylalkyl") - a saturated or wholly or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S; such as, but not limited to pyrrolidine, piperidine, piperazine, morpholine, imidazolidine or pyrazolidine;

"aroyl" - a C(O)Ar, wherein Ar is as phenyl, naphthyl, or aryl alkyl derivatives, such as benzyl and the like;

"alkanoyl" - a C(O)C_{1-10}alkyl wherein the alkyl is as defined above:

"sulfinyl" - the oxide S(O) of the corresponding sulfide, while the term "thio" refers to the sulfide;

"The term "aralkyl" or "heteroarylalkyl" or heterocyclicalkyl" is used herein to mean an aryl, heteroaryl or heterocyclic moiety as respectively defined above said group connected to C_{1-6} alkyl group as also defined above unless otherwise indicated.

As used herein, "optionally substituted" unless specifically defined shall mean 1-3 of such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C_{1-10} alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; S(O)m alkyl, wherein m is 0, 1

C_{1-10} alkyl, $(CR_{10}R_{20})_{n'}OR_{13}$, $(CR_{10}R_{20})_{n'}S(O)_mR_{25}$, $(CR_{10}R_{20})_{n'}NHS(O)_2R_{25}$, $(CR_{10}R_{20})_{n'}NR_8R_9$, $(CR_{10}R_{20})_{n'}NO_2$, $(CR_{10}R_{20})_{n'}CN$, $(CR_{10}R_{20})_{n'}S(O)_mNR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)R_{13}$, $(CR_{10}R_{20})_{n'}C(Z)OR_{13}$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)NR_{13}OR_{12}$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)R_{13}$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}N(OR_{21})C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}N(OR_{21})C(Z)R_{13}$, $(CR_{10}R_{20})_{n'}C(=NOR_{21})R_{13}$, $(CR_{10}R_{20})_{n'}NR_{10}C(=NR_{27})NR_8R_9$, $(CR_{10}R_{20})_{n'}OC(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)OR_{10}$, 5-($R_{25}$)-1,2,4-oxadiazol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclyalkyl moieties may be optionally substituted;

n' is an integer having a value of 1 to 10;

m is 0 or the integer 1 or 2;

R_3 is Q-$(Y_1)_t$;

Q is an aryl or heteroaryl group;

t is a number having a value of 1, 2 or 3;

Z is oxygen or sulfur;

n is 0 or an integer from 1 to 10;

Y_1 is independently selected from hydrogen, C_{1-5} alkyl, halo-substituted C_{1-5} alkyl, halogen, or $-(CR_{10}R_{20})_nY_2$;

Y_2 is $-OR_8$, $-NO_2$, $-S(O)_{m'}R_{11}$, $-SR_8$, $-S(O))_{m'}OR_8$, $-S(O)_mNR_8R_9$, $-NR_8R_9$, $-O(CR_{10}R_{20})_nNR_8R_9$, $-C(O)R_8$, $-CO_2R_8$, $-CO_2(CR_{10}R_{20})_{n'}CONR_8R_9$, $-ZC(O)R_8$, $-CN$, $-C(Z)NR_8R_9$, $NR-NR_{10}C(Z)R_8$, $-C(Z)NR_8OR_9$, $-NR_{10}C(Z)NR_8R_9$, $-NR_{10}S(O)_mR_{11}$, $-N(OR_{21})C(Z)NR_8R_9$, $-N(OR_{21})C(Z)R_8$, $-C(=NOR_{21})R_8$, $-NR_{10}C(=NR_{15})SR_{11}$, $-NR_{10}C(=NR_{15})NR_8R_9$, $-NR_{10}C(=CR_{14}R_{24})SR_{11}$, $-NR_{10}C(=CR_{14}R_{24})NR_8R_9$, $-NR_{10}C(O)C(O)NR_8R_9$, $-NR_{10}C(O)C(O)OR_{10}$, $-C(=NR_{13})NR_8R_9$, $-C(=NOR_{13})NR_8R_9$, $-C(=NR_{13})ZR_{11}$, $-OC(Z)NR_8R_9$, $-NR_{10}S(O)_mCF_3$, $-NR_{10}C(Z)OR_{10}$, 5-(R_{18})-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl;

TITLE OF THE INVENTION

METHODS OF TREATING RAF MEDIATED DISEASES

BACKGROUND OF THE INVENTION

The present invention relates to a method of treating cancer which is effected by raf and raf-inducible genes and proteins.

The *raf* genes code for a family of proteins which can be oncogenically activated through N-terminal fusion, truncation or point mutations. Raf can be activated and undergoes rapid phosphorylation in response to PDGF, EGF, insulin, thrombin, endothelin, acidic FGF, CSF1 or TPA, as well as in response to oncoproteins v-fms, v-src, v-sis, Hras and polyoma middle T antigen.The raf family of oncogenes encompasses human A-raf-1, B-raf-1 and C-raf-1. The A-raf-1 gene is located on chromosome Xp11.3 and is expressed in numerous tissues and tissue types. It encodes a cytosolic protein of approximately 68,000 daltons. The C-raf-1 gene is located on chromosome 3p25 in a chromosomal site that has been found to be altered in several epithelial cancers. The gene encodes a protein which is approximately 74,000 daltons.

There is evidence that raf genes function downstream of ras in the transduction of activation signals from the membrane to the nucleus. By inhibiting raf as described herein, diseases in which ras, raf and other oncogenes integral to the transduction pathway can be effectively treated.

The compounds of the present invention demonstrate anti-cancer activity through the antagonism of RAF kinase .

Antisense constructs which reduce cellular levels of c-Raf, and hence Raf activity, inhibit the growth of oncogene-transformed rodent fibroblasts in soft agar, while exhibiting little or no general cytotoxicity. Since inhibition of growth in soft agar is highly predictive of tumor responsiveness in whole animals, these studies suggest that the antagonism of RAF is an effective means by which to treat cancers in which RAF plays a role.

Examples of such cancers, where RAF is implicated